

Novel MOF/Aerogel Composites (MOFACs) for Drug Delivery Purposes

by

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Novel MOF/Aerogel Composites (MOFACs) for Drug Delivery Purposes

Koç University

Graduate School of Sciences and Engineering

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To my family
Nil, Kerem & Ömer

ABSTRACT

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Composites of MOFs and aerogels (MOFACs) are a new class of nanostructured materials attracting increasing attention due to their favorable properties. The combination of micro-/mesoporosities of MOFs with meso-/macroporosities of aerogels makes MOFACs hierarchically multimodal porous materials. MOFACs with their high surface areas, combined morphological, mechanical, physicochemical and functional properties of both MOFs and aerogels have demonstrated outstanding performances in various applications. In the field of drug delivery, MOFs and aerogels have both been investigated extensively. Combining bimodal porosity and functionality of both MOFs and aerogels is a promising area for drug delivery applications.

In this study, novel Metal-Organic Frameworks/Aerogel composites (MOFACs) comprised of different types of MOFs (Fe-BTC, ZIF-8 or UiO-66) and calcium alginate were synthesized. Spherical bead shaped composites were obtained by incorporating microporous MOFs into meso- and macroporous aerogel matrix by simple mixing combined with dripping technique. The composites were characterized with nitrogen sorption, XRD, SEM and FTIR. The nitrogen adsorption study showed that the MOFACs synthesized had achieved hierarchically macro-, meso- and micro porosities and MOFs micropores were open and accessible. XRD analysis revealed that the MOFs were intact and in crystalline form. FTIR study showed that the MOF and alginate matrix formed a physical mixture in the composite.

The synthesized composites were further loaded with two different drugs paracetamol (acetaminophen) or ibuprofen. Paracetamol was loaded from ethanolic solutions via SAS (supercritical antisolvent precipitation) inside the pores whereas ibuprofen was loaded from supercritical CO₂ solutions. The factors that affect the loading amount and distribution of the drug inside the composite matrix were investigated. Paracetamol loadings were found to be highly dependent on and limited by the drug concentration in ethanolic loading solutions as well as having excess solutions in the extraction vessel prior to supercritical drying. Almost 70 wt% paracetamol loadings were achieved with 1.2 M loading solutions and having excess solutions. Around 20 wt% ibuprofen loadings were achieved from supercritical CO₂ solutions.

The release behavior of the drugs from the composite matrices to PBS buffer or distilled water were investigated. It was shown that the Fe-BTC/Alginate composites were promising for paracetamol delivery and ZIF-8/Alginate composites were found to be promising for ibuprofen delivery as both systems achieved delayed drug delivery with increasing amounts of MOF content in the composites.

Lastly, all release kinetics were fitted into Korsmeyer-Peppas model. It was found that Fickian diffusion is the main transport mechanism while some PBS systems with excess solutions also showed swelling behavior.

ÖZETÇE

Metal-Organik Kafes (MOF)/ Aerojel Kompozitlerinin (MOFACların) İlaç Salınımında Kullanımı

Zeynep İnönü

Kimya ve Biyoloji Mühendisliği Doktora

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Yeni tür nanoyapılı malzemelerden Metal-Organik Kafes (MOF)/Aerojel kompozitleri (MOFAC) elverişli özellikleri sayesinde her geçen gün dikkatleri çekmektedir. Mikro-/mezogözenekli MOF'ların mezo-/makrogözenekli aerojellerle kombinasyonu hiyerarşik olarak farklı gözenekleri birleştirmektedir. MOFAC'lar, yüksek yüzey ölçümleri, kombine morfolojileri, mekanik, fizikokimyasal ve fonksiyonel özellikleri sayesinde birçok uygulamada göze çarpan performanslar sergilemektedir. İlaç salınımı konusundaysa hem MOF'lar hem aerojeller ayrı ayrı sıkça araştırılmaktadır. Çok modlu gözenek kombinasyonlu MOFAC'lar ise ilaç salınımı konusunda umut vadetmektedir.

Bu çalışmada 3 farklı MOF (Fe-BTC, ZIF-8 ya da UiO-66) ve kalsiyum aljinattan oluşan MOFAC'lar sentezlendi. Mikrogözenekli MOF'lar, mezo ve makrogözenekli aerojel matrislerinin içine basit karıştırma ve damlatma teknikleri kullanılarak dahil edildi ve bu şekilde küre boncuk şeklinde kompozitler elde edildi. Sentezlenen kompozitler, azot adsorpsiyonu, XRD, SEM ve FTIR ile karakterize edildi. Azot adsorpsiyonu çalışması, sentezlenen MOFAC'ların hiyerarşik olarak makro-, mezo- ve mikrogözenekli olduğunu, MOF'ların mikrogözeneklerinin açık ve ulaşılabilir olduğunu ortaya koydu. XRD analizi MOF'ların zarar görmediğini ve kristal yapıda kaldığını gösterdi. FTIR analizi ise MOF ve aerojellerin kompozit içerisinde fiziksel bir karışım oluşturduğunu gösterdi.

Sentezlenen kompozitlere daha sonra parasetamol veya ibuprofen ilaçları yüklendi. Parasetamol, etanollü solüsyonundan SAS (süperkritik antisolvent çökmesi) ile gözeneklerin içerisine yüklenirken, ibuprofen süperkritik CO₂ solüsyonundan yüklendi. Yüklenen ilaç miktarını ve ilacın kompozit içerisinde dağılımını belirleyen faktörler araştırıldı. Parasetamol yüklemelerinin ilacın etanol içindeki konsantrasyonuna hayli bağlı olduğu ve bununla da limitli olduğu gözlemlendi. Ayrıca süperkritik kurutma öncesi ekstraksiyon kabına konan fazlalık ilaç solüsyonunun da yükleme miktarında önemi olduğu gözlemlendi. 1.2 M yükleme solüsyonu ve fazlalık solüsyon kullanımı ile ağırlık olarak yaklaşık %70 parasetamol yüklendi. Süperkritik CO₂ solüsyonundan ise ağırlık olarak % 20 ibuprofen yüklemesi gerçekleştirildi.

Daha sonra ise yüklenen ilaçların PBS tampon çözeltisine veya suya salınımları araştırıldı. Fe-BTC/aljinat aerojel kompozitlerinin parasetamol salınımında, ZIF-8/aljinat aerojel kompozitlerinin ise ibuprofen salınımında umut vadettiği gözlemlendi. Kompozitlerin içinde artan MOF miktarı salınımın yavaşlamasını sağladı.

Son olarak, salınım kinetikleri Korsmeyer-Peppas modeli kullanılarak incelendi. Ana salınım mekanizması olarak difüzyon görülmüş, bazı PBS'e salınan fazlalıklı sistemlerde şişme de gözlemlenmiştir.

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ABBREVIATIONS

ε	Porosity
ρ	Density
ATR	Attenuated Total Reflectance
Alg	Alginate Aerogel
BET	Brunauer–Emmett–Teller method
CUS	Coordinatively Unsaturated Sites
C_{pc} in EtOH	Concentration of Paracetamol in Ethanol
C_{drug}	Concentration of Drug
FTIR	Fourier-transform infrared spectroscopy
HPLC	High Performance Liquid Chromatography
IBU	Ibuprofen
MOF	Metal Organic Framework
MOFAC	MOF/Aerogel Composite
M_t	Cumulative amount of drug released at time t
M_∞	Cumulative amount of drug released at infinity
m_{drug}	Mass of drug
$m_{drug-MOFAC}$	Mass of drug loaded MOFAC
m_{MOFAC}	Mass of MOFAC
k	A constant in Peppas' Equation
t	Time
n	Diffusional release exponent
MW_{PC}	Molecular weight of Paracetamol
PBS	Phosphate-buffered saline
PC	Paracetamol
SAS	Supercritical Antisolvent Precipitation
scCO ₂	Supercritical Carbon dioxide
SEM	Scanning Electron Microscope
V_{beads}	Volume of beads
V_p	Pore Volume
V_{sol}	Volume of Solution

XRD	X-ray Diffraction
Zn-Alg	Zinc Alginate Aerogel



Chapter 1: Introduction

Porous materials are increasingly contributing to the developments in many diverse fields ranging from electronics to drug delivery. According to IUPAC (International Union of Pure and Applied Chemistry), materials with pore sizes smaller than 2 nm are classified as microporous, materials with pore sizes between 2 to 50 nm are classified as mesoporous and materials with pore sizes larger than 50 nm are classified as macroporous. Materials that contain multimodal interconnected pores are called hierarchically porous structures (X.-Y. Yang et al., 2017). Structural hierarchy may be bimodal such as micro-micro, micro-meso or micro-macroporous or they can be multimodal like micro-meso-macroporous. These materials which mimic natural systems have enhanced properties and/or they perform multiple functions. For example, combined micro-/mesoporosities lead to high surface areas, high active site accessibilities, short diffusion paths and low mass transport limitations that make them perfect candidates for applications in tissue engineering and drug delivery (X.-Y. Yang et al., 2017), catalysis (Parlett, Wilson, & Lee, 2013), energy conversion and storage (Y. Li, Fu, & Su, 2012), adsorption and separation (Sun et al., 2016). One such strategy for obtaining hierarchical multimodalities is combining two materials which have two different nanoporous structures.

Two remarkable classes of nanostructured materials are aerogels and metal organic frameworks (MOFs). Aerogels were first synthesized in 1932 by Kistler by replacing the liquid in a gel without collapsing its porous network. These synthetic materials which are prepared by special drying techniques have extremely low densities which can be as low as 0.16 mg/cm^3 and have extremely high porosities which can be as high as 99,9%. Because of their high porosity, aerogels are sometimes termed “solid air”. This high porosity results from the internal solid nanostructure of aerogels consisting of cross-linked polymeric nanoparticles with a large fraction of air filled pores. The size of these pores which can be tuned are in the mesopore range and the pore size distribution can be very sharp. Kistler synthesized many different types of inorganic and organic aerogels such as silica, alumina, gelatin and egg albumin (Kistler, 1932). Since then, aerogels have been used in some niche and low volume applications such as components of Cherenkov detectors and space shuttle tiles which utilized silica aerogels due to their

superior thermal insulation performances. With the growing importance of saving energy, research efforts were concentrated on developing products which contained aerogels with superior thermal insulation properties than the conventional products in the market. Blankets made from silica aerogels with thermal conductivities as low as 15 mW/mK were developed by Aspen Aerogel and a plant was constructed to produce them on the large scale which started operation in 2007. Cabot Corporation developed silica aerogel granules under the trade name of Nanogel[®] with excellent insulation, water-repelling, and light transmittance properties for use in glazing systems for energy-efficient daylighting. This was followed by the development of organic polyurethane aerogels by BASF which is currently marketed with the brand name Slentite. Carbon aerogels are another class of aerogels which are obtained by pyrolysis of the organic aerogels at elevated temperatures under an inert atmosphere. Recently developed graphene aerogels which belong to the class of carbon aerogels have very high electrical conductivities and therefore they are promising candidates as electrodes for electrochemical power sources, for energy storage, catalysis and sensors. Organic aerogels can also be polysaccharide based such as alginate, cellulose or starch. Polysaccharide aerogels are very promising in food and cosmetics industries and drug storage and delivery applications since they are biocompatible and biodegradable. Another advantage of aerogels is that their pore properties can be tuned by changing reactant concentrations and synthesis conditions. However, aerogels have several drawbacks such as poor mechanical properties due to their very high porosities and a rather wide pore size distribution with almost no pores in the micropore region.

Metal organic frameworks (MOFs), also referred as porous coordination polymers, are self-assembled crystal structures which are composed of metal nodes and organic linkers. Although MOFs were discovered back in 1965, they have attracted great interest with the studies of by Omar Yaghi and coworkers since 1999 (Czaja, Trukhan, & Müller, 2009). MOFs are crystalline with well-defined pores and they are obtained using “reticular synthesis” in which the predetermined ordered structures are produced by choosing the appropriate molecular building blocks (Yaghi et al., 2003). The opportunity of creating crystal structures with desired pore sizes and functionality makes MOFs very attractive. With their ordered structures, high pore volumes and large surface areas, MOFs have attracted great interest for a large variety of chemical and biological applications including gas storage and separation (Ma & Zhou, 2010), catalysis (Lee et al., 2009),

sensing (Kreno et al., 2012), drug storage and delivery (Keskin & Kızılel, 2011), energy storage and conversion (Liang, Qu, Guo, Zou, & Xu, 2018). Storage of H₂ and CH₄, selective CO₂ separation from natural gas and flue gas are the most widely investigated applications for MOFs (Czaja et al., 2009; Furukawa, Cordova, O’Keeffe, & Yaghi, 2013). BASF commercialized a small variety of MOFs and small start-up companies have been producing tailor-made MOFs for a wide variety of applications.

In spite of their fascinating properties and industrial potential, MOFs are generally obtained in powder form which may be prohibitive in several industrial applications. Such powders cause mass transfer limitations, high pressure drops and entrainment in packed beds and are difficult to handle due to dust formation (Bueken et al., 2017). In order to avoid this problem, significant efforts are being exhausted to either shape MOFs into free-standing monoliths as metal organic aerogels (MOAs) (Lohe, Rose, & Kaskel, 2009), films (Shekhah, Liu, Fischer, & Wöll, 2011), membranes (Gascon & Kapteijn, 2010) or as composites with porous materials such as polyHIPEs (Schwab et al., 2008; Wickenheisser & Janiak, 2015), foams (Pinto, Dias, & Pires, 2013) or sponges (S. M. Li et al., 2017) which usually end up with micro-/macroporous bimodalities.

Incorporating microporous MOFs into mesoporous aerogel matrices to make MOF/aerogel composites (MOFACs) is one strategy to achieve highly desirable products where hierarchical micro-/mesoporosity can be easily controlled or tuned. Both MOFs and aerogels belong to the class of nanostructured materials, have high surface areas, high pore volumes, high porosities and low densities and therefore they are suitable for similar applications. Some general properties of MOFs, aerogels and their composites are listed in Table 1.1. The multimodal hierarchical structures of MOFACs offer great potential for catalysis, selective sorption and separation, and power applications since mesopores and macropores intensify the diffusion and mass transfer whereas micropores create good interaction between host and guest molecules (Ulker, Erucar, Keskin, & Erkey, 2013).

Consequently, MOFACs have been under extensive investigation in the last decade. These materials are intended to offer advantage of both nanostructured materials with enhanced chemical or physical properties to improve performance in various applications. The rapid increase in the number of publications in this field can be attributed to the combination of superior properties of both materials, controllable micro-/mesoporosity ratio, ease of preparation, control over morphology, single step MOF activation and aerogel formation. Moreover, it has been demonstrated in a number of studies that

incorporation of MOFs enhances the mechanical properties of aerogels.(Jiang, Li, Zhou, Xing, & Zhang, 2018; H. Zhu, Yang, Cranston, & Zhu, 2016)

Table 1.1: General properties of MOFs, aerogels and MOFACs.

	Bulk MOFs	Aerogels	MOFACs
Pore size	Microporous	Mesoporous	Mesoporous and microporous
Structure	Crystalline	Amorphous	Amorphous with or without crystalline domains
Shape	Powder	Powder, monolith, bead, particle, fiber	Powder, monolith, bead, particle, fiber

In this study, 3 MOFs (Fe-BTC, UiO-66 and ZIF-8) and calcium alginate were used to synthesize several MOFACs. The synthesized MOFACs are then loaded with two different drugs paracetamol and ibuprofen and further investigated for drug delivery applications by releasing these drugs to either phosphate buffered saline (PBS) or water.

Synthesis methods of MOFACs are presented in detail in Section 2.1 together with examples from the literature which demonstrate the enhanced structural and morphological properties of these novel materials. The use of aerogels and MOFs for drug delivery purposes are given in Sections 2.2 and 2.3. Mathematical modeling of drug release mechanism is briefly reviewed in Section 2.4. Experimental procedures to synthesize the Fe-BTC/Alginate, ZIF-8/Alginate and UiO-66/Alginate aerogels by combining dripping technique with simple mixing method are presented in detail in Chapter 3. Furthermore, the synthesized composites were characterized by nitrogen sorption, FTIR, XRD and SEM. Drug loading techniques and the drug release methods are also presented in Chapter 3. Experimental results such as drug loading amounts and release rate of the drugs as well as their fittings into mathematical models are given and discussed in Chapter 4. Conclusions are presented along with future insights in Chapter 5.

Chapter 2: Literature Review

2.1 Synthesis Techniques of MOFACs

A MOF/aerogel composite is synthesized by incorporation of MOF into the aerogel matrix where MOF can generally be considered as the dispersed phase and the aerogel matrix is the continuous phase. MOFACs can be shaped into various structures that are obtainable for aerogels such as monoliths, beads, particles and fibers. MOFACs can be prepared using two different methods: direct mixing of pre-synthesized MOF with gel precursors followed by gelation and drying and in situ MOF synthesis inside the pores of the hydrogel or aerogel. These two methods are described in detail in Section 2.1.2 and 2.1.3 together with examples of these materials reported in the literature. Since aerogel synthesis and drying techniques are important aspects of both of these methods, they are described in detail in Section 2.1.1.

2.1.1 Aerogel Synthesis and Drying Techniques

In aerogel synthesis, first wet gels (also called hydrogels) are synthesized using various gelation techniques such as sol-gel method, cross-linking of polymers or freeze-thaw induced gelation. Hydrogels can be synthesized in various forms such as monoliths, beads, particles or fibers using different techniques. The modification of these techniques to synthesize MOFACs is explained in detail under section 2.1.2. The prepared hydrogels are then dried to remove the liquid inside the gel network. When hydrogels are dried under ambient conditions, as the solvent evaporates from the pores of the gel, due to presence of a vapor-liquid interface, huge capillary stresses cause the porous network to collapse. (Şahin, Özbakır, İnönü, Ulker, & Erkey, 2018) The resultant materials are called xerogels. Xerogels usually have high densities, low porosities, cracks and very large volume shrinkage. However, with special drying techniques such as supercritical drying or freeze drying, the liquid inside the hydrogel is removed and replaced by air while preserving the original gel structure to obtain aerogels. With both techniques, the liquid-vapor interface and capillary pressures are avoided so that gels are dried to aerogels while preserving their high pore volume.

In supercritical drying, the solvent that is present inside the pores of the gel is extracted by another fluid that is above its critical temperature and pressure, which is called a

supercritical fluid. Supercritical CO₂ (scCO₂) is widely used for this purpose as it is non toxic and has mild critical conditions. To use this technique, the solvent inside the pores has to be miscible or partially miscible in scCO₂. If the solvent is not scCO₂ miscible like water, then it is exchanged by another solvent like ethanol that is miscible in scCO₂. Supercritical drying time is an important consideration for industrial scale application and varies directly with the thickness of the gel. For small particles, supercritical drying of the gels takes about minutes. Commercial supercritical driers with various capacities are available from manufacturers such as Natex and Uhde which can also be used to produce MOFACs. Ambient temperature subcritical drying with high pressure liquid CO₂ is another technique that is widely used. However, after drying subcritically, during depressurization, a vapor-liquid interface cannot be avoided therefore the pores may collapse depending on the surface tension of CO₂ at high pressures, the size of the pores and the strength of the solid matrix.

In freeze drying, the solvent inside the pores is removed by lowering the temperature below freezing point and pressure below sublimation pressure so that the solvent sublimates inside the pores. Aerogels that are obtained by this method are generally called cryogels. Freezing of the solvent molecules may sometimes induce crystal growth inside the pores which results in the formation of macropores, especially if the solvent is water since water expands during freezing. Solvent exchange may also be carried out to prevent this effect. Freeze drying is also an established technology used on an industrial scale.

2.1.2 Direct Mixing Method

In the direct mixing method, the procedure for synthesis of a particular aerogel as described in the preceding Section 2.1.1 is modified by the addition of MOF particles either to the liquid precursor solution or to the sol before gelation as shown in Figure 2.1. Gelation of the matrix entraps the dispersed MOF in the gel and this step is followed by supercritical drying or freeze drying to obtain hierarchically porous hybrid MOFACs.

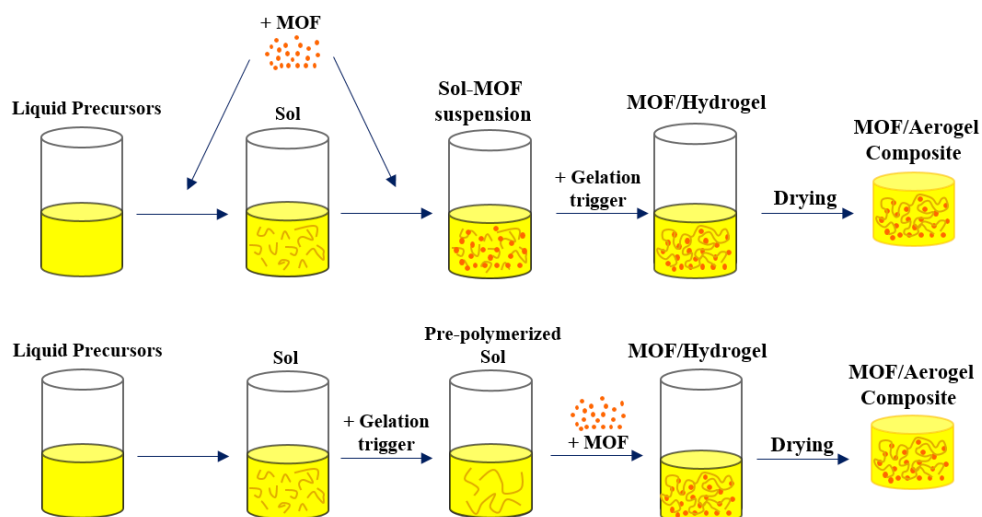


Figure 2.1: MOFAC preparation by MOF incorporation into gel matrices using direct mixing method.

Three common methods used for the synthesis of MOFACs as monoliths, small particles, beads and fibers are shown in Figure 2.2. Monolithic composites are formed by first mixing the gel precursor in an appropriate solvent. Followed by the introduction of MOF powder and homogenization, gelation is induced by the addition of a gelation trigger and the matrix is allowed to gel in a mold which will give the overall shape of the composite. The choice of the material of the mold is as important as the preparation conditions in order to obtain a crack-free MOFAC monolith. The mold should not stick to the gel surface allowing easy release, and also should not interact with the sol before and after the gelation. Teflon and polypropylene molds are better compared to glass molds. Moreover, the surface of the mold should be very smooth since molds with high surface roughness leads to aerogels with increased surface irregularities (Ulker & Erkey, 2014b). Sometimes, gels are aged to increase their mechanical strength. The last step is the removal of the solvent from the pores of the gel.

Micron to millimeter sized particles can be prepared with emulsion gelation method where the sol-MOF suspension can be dispersed in an oil phase to make water in oil (w/o) emulsion (Poncelet et al., 1992). A surfactant may be added to achieve a fine dispersion of sol in oil phase, stabilize the emulsion and decrease the particle size. Ratio of the dispersed to continuous phases, concentration and type of surfactant, geometrical parameters such as mixer shape and diameter, physical parameters like density and viscosity, process parameters such as stirring rate are some of the important parameters

that determine the particle size distribution and particle shapes (Alnaief & Smirnova, 2011). From these parameters, stirring rate is the easiest parameter to control and increasing stirring rate results in smaller sized microspheres. Viscosity of the phases and stirring rate are important parameters for obtaining particles with a narrow size distribution.

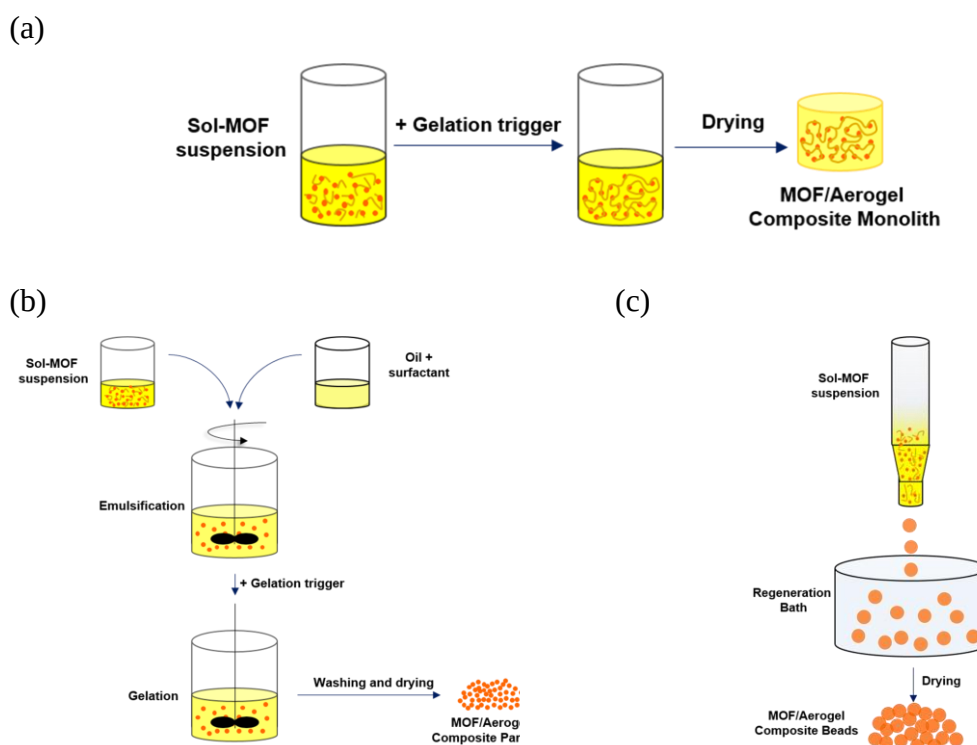


Figure 2.2: Scheme of (a) monolithic MOFAC synthesis in molds, (b) emulsion gelation method to make micron sized particles, (c) dripping method to make spherical beads or fibers.

Spherical beads and fibers can be synthesized by addition of sol-MOF suspension into a gelation bath that induces cross-linking. If the solution is added dropwise, spherical beads are produced (Mike Robitzer, David, Rochas, Di Renzo, & Quignard, 2008). The gelation bath is stirred gently but continuously to avoid agglomerations. Spheres with approximately 5 mm diameter can be produced with this method. The size of the drops depends greatly on the diameter of the nozzle. This technique is used on the industrial scale for production of various types of hydrogel beads. If the solution is added as a continuous stream, fibers can be drawn (Karadagli et al., 2015). Based on this method, it is possible to synthesize periodic aerogel microlattices via 3D printing technique (C. Zhu

et al., 2015).

The direct mixing method was first used by Ulker et al. (Ulker et al., 2013) to synthesize a monolithic MOFAC by incorporating a microporous MOF, Cu-BTC (copper benzene-1,3,5-tricarboxylic acid, HKUST-1) into silica aerogel. Composites with different MOF concentrations were synthesized with a modified two-step sol-gel method which is composed of dispersing Cu-BTC inside a TEOS (tetraethylorthosilicate) and ethanol solution followed by hydrolysis and condensation reactions leading to gelation. The solutions were poured into a mold just before gelation. After the aging step and solvent exchange, the composite gels were supercritically dried to form Cu-BTC/silica aerogel composites which were comprised of microporous Cu-BTC domains embedded in mesoporous silica aerogel network. The gelation time of the composites was observed to increase with increasing MOF content. As FTIR (Fourier-transform infrared spectroscopy) spectra showed no significant change in the chemical structure of silica aerogel, the delay of gelation time was attributed to the change in sol concentration with their adsorption on MOF particle surfaces and formation of the network around the MOF particles retarding the network formation in solution. Although Cu-BTC is prone to decomposition when in contact with water, the XRD (X-ray diffraction) spectra revealed that crystal structure of Cu-BTC remained intact as the composite contained the characteristic peaks of pure crystalline Cu-BTC. BET (Brunauer–Emmett–Teller) results indicated an increase in specific surface area and micropore volume with increasing MOF content but with a slightly lower ratio which is probably due to the small fraction of micropore blockage.

Clogging of MOF micropores by monomers and small oligomers of the gel precursors is undesirable. In order to prevent micropore blocking, pre-polymerization of the gel precursors was suggested (Nuzhdin et al., 2016; Wickenheisser, Herbst, Tannert, Milow, & Janiak, 2015). Since larger oligomer chains are less prone to diffuse into the pores of MOF and block its pores, by pre-polymerizing the precursors, MOF pores can thus be protected. Cu-BTC/silica aerogel monoliths were synthesized by Nuzhdin et al. by adding Cu-BTC as a suspension in isopropanol into pre-synthesized sol just before gelation to preserve the MOF structure and to prevent blockage (Nuzhdin et al., 2016). It was reported that micropore volume and ratio of micropore surface area to BET surface area were directly proportional to Cu-BTC weight percent meaning that Cu-BTC micropores were not blocked at all. Another strategy to prevent pore blocking and achieve

a more homogeneous distribution of MOF particles inside the gel network was suggested by Wickenheisser et al (Wickenheisser et al., 2015). According to their study, addition of a small amount of extra water formed an aqueous layer around the MOF and prevented pore blockage. These water added composites resulted with higher BET surface areas than estimated values for their MOF/xerogel composites.

Direct mixing method may also result in clogging of aerogel pores. For example, Ramasubbu et al. prepared a Cu-BTC/titania aerogel composite by dispersing Cu-BTC into titania sol and experienced a decrease in BET surface area with increasing Cu-BTC content (Ramasubbu, Alwin, Mothi, & Sahaya Shajan, 2017). SAXD (small angle X-ray scattering) results revealed the structural integrity of Cu-BTC in titania aerogel network even after exposure to aqueous medium and ammonia vapors during the synthesis. The reduction of surface area was attributed to the clusters of Cu-BTC blocking the TiO₂ aerogel pores.

Apart from inorganic aerogels, composites of MOFs with biodegradable organic aerogels were also prepared. Zhu et al. incorporated several MOFs into cellulose aerogels (H. Zhu et al., 2016). The composites were synthesized by mixing and entrapping MOF in cellulose nanocrystal (CNC) to form a stable colloidal suspension which was then cross-linked to carboxymethyl cellulose (CMC) that formed a gel. Followed by freeze drying, MOF/cellulose aerogel composites were obtained with various MOFs such as ZIF-8, UiO-66 and MIL-100(Fe). The resultant composites were uniform, flexible and mechanically robust. The hierarchical multimodal pore structure consisted of micropores of MOFs, mesopores between the cross-linked CNC and CMC which make up the walls of the structure and macropores that were formed due to growth of ice crystals during freeze drying. It was observed that the MOF particles were dispersed within the walls with no agglomerate formation.

Generally, it is desirable to achieve a fine dispersion of MOF particles in the gel matrix. Just before the formation of a gel, MOF particles should be well dispersed in the solution without any concentration gradients. This can be accomplished by constant stirring of the solution. Although some MOFs are easily dispersed in gel medium, agglomerates of MOFs are obtained especially in highly viscous solutions and at high MOF loadings. This leads to inhomogeneous distribution of MOF particles inside the aerogel matrix. These agglomerations of MOF clusters can be a reason of reduction of interconnected continuous porous network structure thus result in collapse of the

structure. For example, ZIF-8/konjac glucomannan (KGM) aerogel composites were synthesized via sol-gel method (Yuan et al., 2018). The effect of MOF loading on the composite morphology was studied. At low MOF concentrations (7:5 KGM/ZIF-8 ratio), a good dispersion and uniform porous structure was observed. With increasing MOF concentration (such as 7:7.5 KGM/ZIF-8 ratio), agglomeration of excess ZIF-8 particles lead to asymmetrical MOF distribution, a non-uniform pore distribution and eventually collapse of the porous network.

MOF/graphene aerogel composites were studied by several groups due to the fact that both MOFs and graphene aerogels are promising materials for similar applications such as energy storage and adsorption and their synergistic effect may lead to the development of superior materials. Graphene is an attractive material due to its high surface area, mechanical, thermal and chemical stability. Graphene aerogel which is a 3D network of 2D graphene sheets is especially promising to support MOFs. Graphene aerogels are generally synthesized by first forming an aqueous solution of graphene oxide (GO) prepared using methods such as Hummer's method (Hummers & Offeman, 1958). MOF particles or suspensions can be easily mixed with GO solution at this step. After gelation, the hydrogel is then dried either by supercritical drying or freeze drying to obtain MOF/graphene aerogel composites. GO can be reduced either before or after the drying step.

Zhang et al. synthesized MIL-101(Cr)/graphene aerogel (GA) composites (X. Zhang, Liang, Han, Wan, & Ding, 2016). They mixed MIL-101 into a graphene oxide (GO) dispersion, freeze dried the resulting gel and reduced GO under hydrazine vapor. MIL-101 particles were immobilized on GO sheets which was attributed to the interaction between positively charged coordinatively unsaturated metal sites of MIL-101 and negatively charged GO sheets. This immobilization prevented the agglomeration of MIL-101 particles and improved their dispersion on graphene sheets.

Mao et al. synthesized ZIF-8/reduced graphene oxide (rGO) aerogel with a one-step self-assembly method where metal sites of MOFs were used synergistically for chemical reduction and cross-linking (Mao et al., 2017). ZIF-8 was first dispersed in methanol and then added to an aqueous solution containing GO nanosheets and hydrazine hydrate. GO sheets acted as binding sites for ZIF-8 and Zn^{2+} ion of ZIF-8 acted as a coordinator for removal of hydrophilic groups such as carboxyl, hydroxyl and epoxy groups of graphene oxide (GO), therefore accelerated the gelation process of GO nanosheets by metal-oxygen

covalent bonding. Followed by freeze drying, ZIF-8/reduced graphene aerogel (rGA) was obtained with enhanced mechanical properties and superhydrophobic nature with high water repellency and oil adsorption capacity. SEM images revealed that ZIF-8 crystals were uniformly distributed on rGO walls containing micro-/macropores. FTIR analysis showed that ZIF-8 was deposited on the rGO aerogel and the covalent bond of Zn–O between ZIF-8 and rGA was observed in both the FTIR and Raman spectra.

Similarly, Xu et al. mixed a wide variety of MOFs in graphene oxide (GO) solution where GO sheets and MOFs spontaneously self-assembled into 3D structures to form hydrogels (Xu et al., 2017). Followed by freeze drying, MOFACs were obtained which included Ni-MOF, ZIF-8, MOF-5, Sn-MOF, Co-MOF and bimetallic Fe-MOF/Ni-MOF. Li et al. also synthesized Zr-MOF(MMU)/graphene aerogel in the form of a disk for use in solid phase extraction (SPE) (G. Li, Pang, Wu, & Ouyang, 2018). The SEM images showed that the honeycomb-like structure of pure graphene aerogel was conserved but the smooth GA walls became rougher when MMU was wrapped around the graphene aerogel. However, XRD pattern revealed that the composite lost several characteristic peaks of MMU which was attributed to the change in the MMU crystal structure after being incorporated into GO matrix.

Taking advantage of amphiphilic nature of MOFs and GO, Zhang et al. synthesized Zr-MOF/GO composites by forming a pickering emulsion in which Zr-MOF (Zr-BDC-NO₂) and GO solids interacted with hydrogen bonding and accumulated at the water-oil interface (F. Zhang et al., 2017). When the emulsion of oil droplets dispersed in water phase was freeze dried to remove the oil and water, a micro/macroporous solid composite was obtained. The droplets of the emulsion were used as the template of composite pores and the pore sizes of the composites were consistent with the emulsion's droplet sizes. The effect of MOF concentration on pore size was investigated. It was found that with increasing MOF content, average droplet size of the emulsion first decreased and then increased. The decrease in droplet size was attributed to the increase in emulsifier amount. Subsequent increase in droplet size was described by the strengthening of the interactions between Zr-BDC-NO₂ and GO at higher concentrations which resulted in reduction of amphiphilicities of both emulsifiers.

Other than monoliths, micron sized particles can be prepared with emulsion gelation method as explained previously. Shalygin et al. synthesized Cu-BTC/silica aerogel particles by coupling sol-gel method and emulsion gelation method (Shalygin, Nuzhdin,

Bukhtiyarova, & Martyanov, 2017). By dispersing Cu-BTC powder inside silica sol and dispersing this suspension in an oil phase which consisted of pentadecane, a water in oil emulsion was formed under continuous stirring. The droplets were composed of the dispersed phase therefore the gelation of the particles took place inside the emulsion. Followed by washing to remove pentadecane, the composite particles were dried via supercritical drying. Two different pellet sizes (0.1-0.5 mm and 1-2.5 mm) were formed by changing the stirring rate of the emulsion (which were 380 and 250 rpm, respectively).

An important consideration in synthesis of MOFACs is the compatibility of MOFs with the solvents used in aerogel synthesis. Since most aerogels are synthesized in aqueous solutions, MOFs should be stable in water during the synthesis stage. It is well known that the oxygen in water is a nucleophile whereas the metal coordination centers in MOFs are electrophilic. If this metal center of MOF is not sufficiently inert, water can coordinate with the metal cluster and distort or destroy the MOF's crystal lattice structure. Calculation of the free energy change of this hydrolysis reaction may enable one to predict if such a distortion is thermodynamically favorable for a particular MOF. Kinetic factors may also play a role and the activation energy for this reaction may be high due to the steric factors or for hydrophobic MOFs. The degree of stability of a wide variety of MOFs in aqueous solutions are tabulated in an excellent study by Burtch et al. which can be used as a guideline before starting to develop MOFACs for a particular application (Burtch, Jasuja, & Walton, 2014).

Solvent exchange is another step in aerogel synthesis where MOFs are subjected to solvents such as acetone or ethanol that can be removed by supercritical drying. Studies in the literature on stability of MOFs in such solvents are not extensive. Another important consideration in direct mixing method is the interference of MOFs with the polymerization chemistry for gel formation. The procedures that are developed for synthesis of pure gels/aerogels may not work in the presence of MOF in solution or may lead to a different pore structure than pure gels. This may be due to the effects of adsorption of sol-gel or cross-linking catalysts and monomers on the surface of MOFs which change catalyst and reactant concentrations as well as pH. It is also well known that MOFs can function as catalysts and can influence the delicate reaction network for the formation of gels. Studies are required on how the addition of MOF to precursor solution for gel synthesis affect the gelation behavior. As there are many different MOFs and aerogels that can be combined, selecting a synthetic procedure for a MOFAC that

will preserve the properties of pure MOF and pure aerogel can be difficult. Each composite should be approached with great attention where its functionality and stability should be checked with various characterization techniques such as XRD and N₂ sorption analysis.

2.1.3 *In situ MOF Synthesis*

The other technique to prepare MOFACs is synthesizing the MOF in situ inside the pores of an aerogel or inside the pores of a gel which is then dried. This method can also be termed as ship-in-a-bottle approach where the MOF is the ship and bottle is the pore of gel.

MOFs can be synthesized at ambient conditions or at high temperatures or pressures by various techniques such as conventional heating, microwave heating, electrochemistry, mechanochemistry and ultrasonic methods primarily by reactions of metal precursors and organic linkers (Stock & Biswas, 2012). Then the synthesized MOFs are purified and activated which generally is associated with removal of the solvent from the pores of the MOF. For a detailed description of synthesis techniques of MOFs, excellent reviews are present (Bosch, Yuan, Rutledge, & Zhou, 2017; Férey, 2008; Furukawa et al., 2013; Rubio-Martinez et al., 2017; Stock & Biswas, 2012). Using the mentioned techniques, MOFs can be grown either inside the pores of a hydrogel or an aerogel by sequentially adding the metal precursor and the organic linker as depicted in Figure 2.3. For synthesis in hydrogels, MOF precursors are incorporated to the hydrogel thus MOFs are grown in situ inside the pores of hydrogel followed by drying to obtain MOFACs. Whereas for synthesis in aerogels, plain gels are synthesized and dried supercritically or via freeze drying. Then the as-synthesized aerogels are immersed in MOF precursor solutions to synthesize MOF inside the pores of the aerogel, preferably followed by another drying to obtain MOFACs.

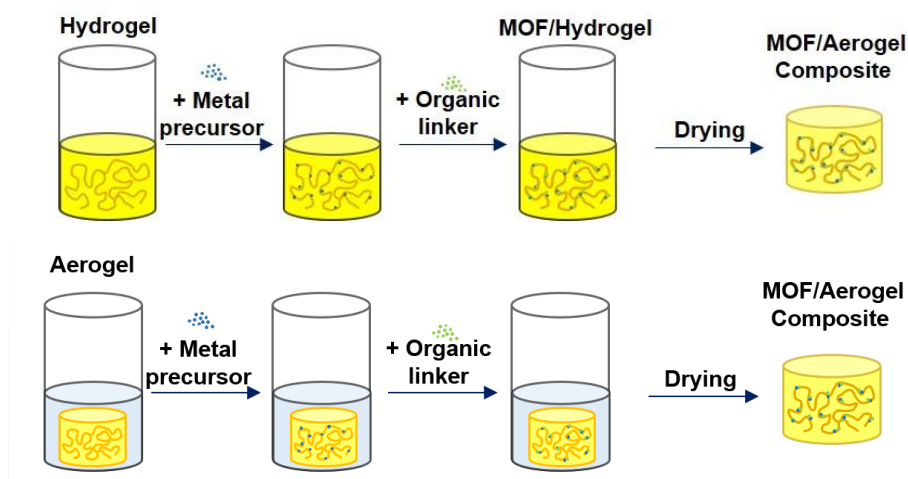


Figure 2.3: Preparation of MOFACs in situ on hydrogels and aerogels.

Either using hydrogel or aerogel as substrate, when the necessary conditions are reached for the start of the reaction between metal precursor and organic linker, MOF crystals begin forming, nucleating, growing and precipitating both inside and outside the porous matrix. Next is the purification step which is the removal of unreacted precursors and unbound MOF particles. If MOFs are grown without binding, they are susceptible to be washed out during purification steps. Therefore, binding of MOFs to the gel matrix is highly desirable in this technique. MOFs can be attached to internal surface of gel matrices via interaction between the functional groups of gels and metal ions of MOFs. This way, with the addition of organic linker, already attached metal ions start reacting with the organic linker and nucleating on the attached site. Several groups took advantage of substrates that already contain surface functional groups like graphene oxide whereas some others functionalized their substrates prior to MOF growth. Another strategy is entrapping metal ions of MOF or MOF particles themselves in gel matrix to prevent losses during purification. Even using the metal sites of aerogel for MOF growth is possible. The last step is the removal of solvent from the pores of the MOF and the gel. This is an important step as it facilitates high surface areas. For general MOF synthesis, supercritical activation is considered as a comparably gentler method that retains the potential porosity as conventional methods may result in collapse of the porous network (Bosch, Zhang, & Zhou, 2014). Fortunately, during in situ MOF synthesis, aerogel formation and MOF activation can be accomplished in a single step either by supercritical drying or freeze drying methods.

Wisser et al. formed Cu-BTC crystals in hollow fibers of chitin by taking advantage

of high affinity of biopolymer to the metal ions (Wisser et al., 2015). Chitinous networks that were extracted from a marine sponge were immersed in a solution containing Cu metal precursor $\text{Cu}(\text{NO}_3)_2$ and then organic linker BTC (benzene-1,3,5-tricarboxylic acid) was added. As the functional groups of proteins interacted with metal ions, chitin-copper interactions resulted in MOF nucleation mainly inside the hollow fibers of chitin creating a hierarchical porous structure. After MOF formation, unbound MOFs were washed and then the matrix was dried supercritically. The MOF loading reached up to 55% with surface areas up to $800 \text{ m}^2/\text{g}$ and pore volumes of $3.6 \text{ cm}^3/\text{g}$.

Bo et al. synthesized ZIF-8/cellulose aerogels by first dispersing zinc precursor $\text{Zn}(\text{NO}_3)_2 \cdot 6\text{H}_2\text{O}$ into cellulose solution (Bo et al., 2018). Then by chemically cross-linking the polymer with N,N'-methylenebisacrylamide (MBA), a cellulose hydrogel was formed where Zn^{2+} ions were trapped inside. Followed by freeze drying, Zn^{2+} /cellulose aerogels were obtained. Then this aerogel was immersed into organic linker 2-methylimidazole solution to start MOF growth. The composite was washed and freeze dried to obtain ZIF-8/cellulose aerogel. PXRD revealed that the crystallinity of ZIF-8 was preserved in the composite and FTIR exhibited the characteristic peaks of both ZIF-8 and cellulose aerogel. ZIF-8 contents were determined to be 10-30 wt% by TGA. As the MOF content increased, density increased while the total pore volume and porosity decreased even though the composite with 30 wt% ZIF-8 had 95.3% porosity.

Another in situ ZIF-8 loading on cellulose was performed by Zhu et al. where they synthesized MOF crystals on template of TEMPO (2,2,6,6-Tetramethylpiperidyl-1-oxyl)-oxidized cellulose nanofibrils (CNFs) (L. Zhu et al., 2018). By TEMPO-oxidation, carboxylate groups formed on the surface of CNFs which interacted ionically with multivalent metal ions such as Zn^{2+} , Cu^{2+} or Co^{2+} . When an appropriate organic ligand precursor is also present in the medium, MOF crystals start to nucleate on fibrous CNF networks so that ZIF-8 crystals adhere to cellulose via H-bonding and ionic interactions forming hierarchically porous structures. MOF loadings and size of MOF crystals were controlled with precursor concentrations and temperature.

Moreover, Ren et al. in situ synthesized ZIF-9 and ZIF-12 on pre-synthesized cellulose aerogels by immersing them in MOF precursor solutions (Ren et al., 2018). Same precursors but different solvents were used for ZIF-9 and ZIF-12. The composites were then washed and freeze dried again to obtain ZIF/cellulose aerogel composites. Although no change in porous structure of cellulose aerogel was observed, the shape and

XRD spectra of MOFs grown inside the pores of cellulose aerogels were observed to be different than their pure counterparts and this was attributed to the influence of aerogel surface on the crystal growth.

Composites in the form of microspheres and fibers with channels having honeycomb internal structures were also synthesized by the in situ method (Y. Zhang, Cai, Zhang, Ke, & Zhang, 2018). ZIF-8/chitosan microspheres with such a structure were prepared by adding a mixture of zinc metal ion precursor $\text{Zn}(\text{NO}_3)_2$ and chitosan to a solution of NaOH with organic linker 2-methylimidazole (Hmim). Gelation of chitosan and growth of ZIF-8 crystals occurred instantly and simultaneously. This way, spheres having a diameter of 2 mm and fibers having diameter about 1 mm were synthesized with the dripping technique. ZIF-8 particles were well dispersed and embedded inside the chitosan matrix and their loadings ranged from 30 wt% to 83 wt% which was mainly influenced by the concentration of $\text{Zn}(\text{NO}_3)_2$ precursor. 200 to 500 nm sized ZIF-8 particles were obtained by changing the amount of $\text{Zn}(\text{NO}_3)_2$ precursor concentration without changing the molar ratio of Zn^{2+} to Hmim. Additionally, by changing the metal ion and organic ligand, ZIF-7/chitosan and ZIF-67/chitosan microspheres were also synthesized.

An important substrate to grow MOFs is graphene aerogel. Plentiful functional groups of graphene oxide can well adsorb metal ions and promote heterogeneous nucleation thereby allow formation of uniformly dispersed MOF particles on graphene sheets. There are two strategies for growing MOFs in situ on graphene, either in aqueous graphene oxide suspension or on graphene aerogel.

Liu et al. synthesized two kinds of Fe-MOF/GA composites. They first synthesized spindle-like MIL-88-Fe particles by adding metal and ligand precursors and growing them in situ on presynthesized graphene aerogel (Liu, Yan, Cai, Lin, & Hu, 2018). They also synthesized by first adding Fe^{3+} ions to graphene oxide solution to make Fe^{3+} -doped graphene aerogels which were then subjected to a solution of the ligand. This way, oriented rod-like MOFs were grown directionally and controllably on (002) lattice plane of graphene surface. The interaction between graphene and MOF was stronger for the latter case. Moreover, MOFs were distributed more evenly due to the homogeneous distribution of Fe^{3+} ions on the graphene aerogel surface and the composite had a higher specific surface area. Qu et al. synthesized Cu-BTC on the surface of Ru/3D graphene aerogel surface by step-by-step self-assembly method (Qu et al., 2018). They first

synthesized 3D graphene aerogel with metallic ruthenium particles (Ru/GA) and then modified the surface functional groups of Ru/GA in order to form strong chemical bonds with copper ions. With the addition of copper precursor and the organic ligand several times in succession, they were able to synthesize approximately 30 wt% Cu-BTC on Ru/GA surface as determined by TGA.

Growing MOFs on graphene oxide sheets in aqueous solution is also possible. For example, Yang et al. synthesized ZIF-67 on the residual hydrophilic sites of rGO (Q. Yang et al., 2018). The hydrogel was then freeze dried yielding ZIF-67/rGO aerogel that was cross-linked honeycombs containing micro-/macropores. Method of in situ MOF synthesis was recently extended by two-step reduction and layer-by-layer assembly to synthesize hierarchically micro-/meso-/macroporous ZIF-8/graphene aerogel (Jiang et al., 2018). Firstly, a graphene oxide solution was partially reduced, frozen and thawed, reduced again to yield graphene hydrogel with large pores which was then used as the template. By immersion of hydrogel in both precursor solutions successively, ZIF-8 was synthesized in situ layer-by-layer on both external and internal surface of graphene. As large pores of graphene minimized the capillary forces and the mechanical strength of graphene increased with incorporation of ZIF-8 crystals, composites were able to resist ambient pressure drying without collapse of the porous structure. MOF loadings were strongly dependent on the oxygen containing functional groups of rGO and they were quantified from the density increase and carbon/nitrogen ratio. The ZIF-8 loadings reached up to 88 wt% with 10 immersion cycles and surface area increased up to 1099 m²/g by 8 cycles.

Domán et al. synthesized Cu-BTC/carbon aerogel composites with the aim of increasing the thermal and mechanical stability of Cu-BTC (Domán et al., 2018). For in situ synthesis, carbon aerogel was soaked in metal and ligand precursor solutions successively before the solvothermal process. In order to grow Cu-BTC crystals on the surface of carbon aerogel, the surface was made acidic by the addition of acidic surface groups. However, no chemical interaction between carbon aerogel surface and Cu atoms of Cu-BTC was observed, indicating the composite resembled a physical mixture but the mesopores and macropores of the aerogel was filled with the synthesized MOF.

Another MOF/carbon aerogel composite was prepared by Zhao et al. (Zhao, Chen, Peng, Wang, & Zhao, 2017). They grew MOFs with mixed metal ions on the surface of carbon aerogel to make composites via a modified hydrothermal reaction. By placing

carbon aerogel inside an autoclave along with the MOF precursors, a bifunctional MOF(Fe/Co)/carbon aerogel (CA) was prepared with a good chemical stability. Different Fe/Co ratios were studied, yet only a ratio of 2:1 was found to lead to a successful growth on the surface of carbon aerogel to make MOF(2Fe/Co)/CA composite.

A different approach is growing MOF in situ on other materials which are then incorporated into aerogel as in the recent work of Zhang et al.(W. Zhang et al., 2017). They synthesized ZIF-8 in situ on carbon nitride (C_3N_4) nanosheets and then added them to agar aerogel to increase its flexibility and efficiency for waste water treatment. The maximum dye adsorption capacity was obtained with ZIF-8/ C_3N_4 aerogel which was attributed to the fine dispersion of ZIF-8 on the nanosheets that was achieved by in situ synthesis with an additional benefit of reusability.

A very interesting study was conducted by Reboul et al. who synthesized MOF on a metal oxide aerogel using its metal as a nucleation site (Reboul et al., 2012). By applying a pseudomorphic replacement process which involves dissolution of the metastable parent product and reprecipitation to a new stable phase, a coordination replication was achieved when organic ligands were introduced into a pre-shaped metal oxide. So the metal oxide was not only the metal ion source but also the “architecture-directing agent”. For this, first alumina aerogels (meso and macroporous) were synthesized and an organic linker H_2ndc (2,6-Naphthalenedicarboxylic acid) was added. Followed by microwave treatment, aluminum naphthalene dicarboxylate frameworks were grown using the aerogel as nucleation site, creating MOF crystals into two and three dimensional mesoscopic higher-order structures. FESEM analysis showed the dissolution of the metal oxide phase providing metal ions for MOF synthesis and the formation of MOF crystals on alumina pattern without being connected to each other. The same method was applied with two more dicarboxylic acids as well.

Although a more uniform distribution of MOF crystals inside the composite is achieved with this technique when compared to direct mixing method, MOF growth is not easily controlled. Concentration of precursors and reaction environment such as temperature are generally adjusted to control MOF growth inside the pores. As the amount of MOF synthesized cannot be predetermined in this technique, methods such as TGA (thermogravimetric analysis) and weighing are used to estimate the MOF amount in composite. Another important aspect is the ability of hydrogel/aerogel matrix to maintain its structural integrity against the synthesis conditions and solvents used for

MOF preparation. For example, solvothermal methods will not be applicable to synthesize composites of MOFs with most organic gels as they will degrade at high temperatures. Furthermore, the loss of mesopore volume due to the growth of MOF particles inside the mesopore volume is another consideration. If such a decrease cannot be tolerated for a particular application, then direct mixing method may be a better choice. The advantages and disadvantages of both methods are given in Table 2.1 as a brief summary.

Table 2.1: Advantages and disadvantages of the synthesis techniques of MOFACs.

	Advantages	Disadvantages
Direct mixing method	• No loss of mesopore volume • MOFs entrapped into gel matrix • Controlled MOF loading	• MOF may not be stable during aerogel synthesis • Sol may clog MOF micropores • MOF may effect gelation behavior (interference of MOFs with the polymerization chemistry) • Non-uniform MOF distribution and agglomeration possibility
In situ MOF synthesis	• Uniform MOF distribution • No MOF agglomerations • No MOF pore blockage	• Aerogel may not be stable during MOF synthesis • Loss of mesopore volume • MOF must attach the matrix to prevent loss • Uncontrolled MOF loading

Some representative data from the studies in the literature on pore properties of MOFACs are given in Table 2.2. The increase in surface areas with increasing MOF content is evident which is indicative of preservation of the microporous nature of MOFs in the composite. More details on these properties can be found in the corresponding references given in Table 2.2.

Table 2.2: Comparison of pore and structural properties of some pure MOFs and their MOFACs.

Reference	Material	MOF wt%	Micropore area (m ² /g)	BET surface area (m ² /g)	Pore Volume (cm ³ /g)	Micropore volume (cm ³ /g)	Density (g/cm ³)
Ulker et al., 2013	Pure silica aerogel	0	0	926		0	0.13
	Cu-BTC/Silica Aerogel	4.2	19	1025		0.006	0.142
	Cu-BTC/Silica Aerogel	16.3	59	1036		0.028	0.154
	Cu-BTC/Silica Aerogel	30.5	211	1138		0.11	0.184
	Pure Cu-BTC	100	1119	1352		0.591	0.35
Wisser et al., 2015	Pure chitin network	0		18±9	0.15±0.08		
	Cu-BTC/Chitin Aerogel	53		730±70	3.6±1		
	Pure Cu-BTC	100		1370±20	0.75±0.06		
Jiang et al., 2018	Graphene Aerogel (GA)	0		404		0.52	0.003
	ZIF-8/GA 2 cycles	71.8		663		0.4	
	ZIF-8/GA 4 cycles	73.5		799		0.53	
	ZIF-8/GA 8 cycles	86.7		1099		0.67	
	ZIF-8 pure	100		1567		0.52	0.95
Zhang et al., 2016	pure GA	0		272			
	MIL-101/GA 0,5	33		469.8			
	MIL-101/GA 0,51	50		1126.6			
	MIL-101/GA 0,52	70		1560.1			
Bo et al., 2018	ZIF-8/Cellulose Aerogel	10			32.62		0.047
	ZIF-8/Cellulose Aerogel	15			25.37		0.053
	ZIF-8/Cellulose Aerogel	20			21.54		0.067
	ZIF-8/Cellulose Aerogel	30			19.33		0.076

2.2 Aerogel Based Drug Delivery Systems

Aerogels have been widely studied for drug delivery purposes (Ulker & Erkey, 2014b). Various studies were conducted using biocompatible inorganic silica aerogels as well as organic ones (Caputo, Scognamiglio, & De Marco, 2012; Mehling, Smirnova, Guenther, & Neubert, 2009a; I Smirnova, Mamic, & Arlt, 2003; I Smirnova,

Suttiruengwong, & Arlt, 2004; Irina Smirnova, Suttiruengwong, Seiler, & Arlt, 2004a). Organic polysaccharide aerogels are especially promising due to their biocompatibility and biodegradability. Some examples are alginate, starch, chitosan and cellulose aerogels. Composites of different organic and inorganic aerogels, coatings and membranes on aerogels are also present in the literature (Giray, Bal, Kartal, Kızılel, & Erkey, 2012; Gonçalves et al., 2016; Ulker & Erkey, 2014a; Veres et al., 2017; Veronovski, Knez, & Novak, 2013). Several routes have been employed to load the drugs: incorporation of the drug before the gelation, during aging or through adsorption/precipitation from solutions of supercritical CO₂. Solubility of the drug is the important parameter for the choice of route. Very fast deliveries have been achieved especially for poorly soluble drugs due to the rapid collapse of hydrophilic aerogel matrix and amorphous form of loaded drug (Irina Smirnova, Suttiruengwong, Seiler, & Arlt, 2004b). The releases can also be tailored by hydrophobization of the aerogels (I Smirnova et al., 2004). Temperature or pH responsive release is also possible for some aerogels such as alginate and chitosan (Deng et al., 2010; García-González, Jin, Gerth, Alvarez-Lorenzo, & Smirnova, 2015; Radwan-Pragłowska, Piatkowski, Janus, Bogdał, & Matysek, 2017; Shao et al., 2018).

Several aerogels were studied for loading and delivery of paracetamol or ibuprofen so far. Paracetamol was loaded via SAS (supercritical antisolvent precipitation) process inside the pores of silica aerogel by Ulker and Erkey (Ulker & Erkey, 2015). The release of the drug to phosphate buffered saline (PBS) at pH of 5.8 and under constant stirring at 310 K, an initial burst release was observed related to the collapse of the hydrophilic silica aerogel matrix. The burst phase was then followed by diffusion of the paracetamol from the pores of the remaining small pieces. Similarly, Mehling et al. studied the loading and release of paracetamol from organic polysaccharide aerogels (starch and alginate) and found out that the delivery of the drug was delivered at a short time (in less than 2 hours) from both aerogels due to the fact that paracetamol is readily soluble at that pH (Mehling, Smirnova, Guenther, & Neubert, 2009b). However, ibuprofen loading and delivery was also studied in the same study and it was found that ibuprofen deliveries took much longer time due to the poor solubility of the drug in release medium. The authors also noted that delivery of ibuprofen is also matrix dependent due to the fact that it is adsorbed on a molecular level inside the pores of aerogel matrix.

2.3 MOF Based Drug Delivery Systems

MOFs have been studied in the literature for drug delivery purposes as well as sensing, nitric oxide (NO) storage, and imaging agents (Keskin & Kızılel, 2011). Especially, nanoMOFs with high drug capacities (up to 42 wt %) and prolonged releases (from 3 to 14 days) make these materials very attractive drug carriers (Giménez-Marqués, Hidalgo, Serre, & Horcajada, 2016; McKinlay et al., 2010). The deliveries can be temperature, pressure, pH, magnetically responsive or even multiple stimuli responsive (Wu & Yang, 2017). Metal-biomolecule frameworks (also known as bioMOFs) were also studied in the literature where either the bioactive molecule is used as the linker or a bioactive metal is used as the inorganic part of the MOF (S Rojas, Devic, & Horcajada, 2017). Drugs can be incorporated into MOF pores by encapsulation during synthesis or post-synthesis of MOFs (Lleana, Galve, Rubio, Teñez, & Coronas, 2012). For drug molecules with size larger than the pore apertures, even external surface attachment is possible for nanoMOFs (Vasconcelos et al., 2012).

There are several ibuprofen loaded MOF studies in the literature. Horcajada et al. first loaded ibuprofen on MIL-100 and MIL-101 MOFs (Horcajada et al., 2006). They achieved high drug loadings (0.347 g IBU/g of dehydrated MIL-100 and 1.376 g IBU/g dehydrated MIL-101) and released the drug to simulated body fluid (SBF) medium at 37°C. The complete release of ibuprofen took 3 days and 6 days from MIL-100 and MIL-101, respectively. Later, Horcajada et al. loaded ibuprofen to MIL-53(Cr) and MIL-53(Fe) MOFs (Horcajada et al., 2008) to see the effect of MOF flexibility on drug loading and delivery. The MOFs used were able to adsorb around 20 wt % of Ibuprofen (Ibuprofen/dehydrated MIL-53) from hexane solutions. The delivery of drug was very slow with zero-order kinetics and complete delivery of ibuprofen took 3 weeks. Rojas et al. used (MIL-100(Fe), UiO-66(Zr), and MIL-127(Fe) MOFs to load and deliver ibuprofen as well as aspirin. They used ethanolic solutions for incorporation of the drugs and for delivery, they used aqueous media at 37 °C as simulated cutaneous conditions. The release of the drugs were found to be mainly governed by a diffusion process which is predictable by the Higuchi model except MIL-127@IBU which showed zero- order kinetics. It should be noted that the particle size of the synthesized MOFs were quite small, $\sim 460 \pm 80$ nm for MIL-100(Fe), $\sim 240 \pm 40$ nm for UiO-66 and $\sim 2 \pm 1$ μ m for MIL-127(Fe).

There is a study in literature that uses supercritical carbon dioxide-assisted drug

loading (Matsuyama et al., 2014). They loaded ibuprofen to MIL-53(Fe) and MIL-100(Fe). The study compared 3 loading methods: Conventional ibuprofen loading with conventional drying, conventional ibuprofen loading with scCO₂ drying and scCO₂-assisted ibuprofen loading with scCO₂ drying and found out that using scCO₂ provided greater access to the pores of the MOFs, therefore producing larger pore volumes and higher loading of guest molecules which is very useful for drug delivery applications.

2.4 Mathematical Modeling of Drug Delivery

Mathematical modelling of drug delivery is important to understand the underlying transport mechanisms. One way of modelling drug delivery is the mechanistic realistic mathematical model which is based on equations that describe real phenomena, such as mass transport by diffusion, dissolution of drug and/or excipient particles, and/or the transition of a polymer from the glassy to the rubbery state (J Siepmann & Siepmann, 2008). Usually partial differential equations are to be solved with appropriate boundary and initial conditions. The complexity of the system determines if the solution is analytical or numerical. There are theories based on Fick's law of diffusion, theories that consider polymer swelling, polymer erosion or degradation.

There are also several empirical or semi-empirical models developed over the years to describe different drug release mechanisms from different matrices or geometries and majority of them are based on diffusion equations. First and most well-known model was developed by Higuchi (Higuchi, 1961). He modelled the rate of drug release from an ointment into a perfect sink condition and the simple equation he developed is named after him as Higuchi equation:

$$M_t = k\sqrt{t} \quad (2.1)$$

where M_t is the cumulative amount of drug released from the ointment film at time t , $k = A\sqrt{(2C_{ini}DC_s)}$ where A is the surface area of the film which is exposed to the skin, D is the diffusion coefficient, C_{ini} is the initial drug concentration and C_s is the solubility of the drug.

The classical Higuchi equation shown as Equation 2.1 describes a simple “square root of time” release kinetics but several assumptions must be made. Drug transport through the ointment base should be the rate limiting step, the skin must act like a “perfect sink”, the initial drug concentration should be much higher than the solubility of the drug, the drug should be finely dispersed and homogeneously distributed within the ointment

base, dissolution of the drug should be rapid compared to the diffusion of dissolved drug molecules, the diffusion coefficient of the drug should be constant, edge effects should be negligible and the matrix (ointment base) should not swell or dissolve during drug release (Juergen Siepmann & Peppas, 2011).

Another frequently used empirical model is the Peppas equation of power law given in equation 2.2 (Ritger & Peppas, 1987):

$$\frac{M_t}{M_\infty} = kt^n \quad (2.2)$$

where M_t and M_∞ is the cumulative amount of drug released at time t and at infinity, k is a constant incorporating structural characteristics of the macromolecular network and n is the diffusional release exponent which indicates the transport mechanism such as diffusion or polymer relaxation controlled drug release. This equation can be used for a variety of geometries such as cylinder and spherical systems as well as thin films as in Higuchi equation and n values are indicative of different mechanisms for different geometries and are shown in Table 2.3 (J Siepmann & Siepmann, 2008).

Table 2.3: Diffusional exponent n of Peppas equation and drug release mechanisms for different geometries

Diffusional exponent, n			Drug Release Mechanism
Thin Film	Cylinder	Sphere	
0.5	0.45	0.43	Fickian diffusion
$0.5 < n < 1.0$	$0.45 < n < 0.89$	$0.43 < n < 0.85$	Anomalous transport
1.0	0.89	0.85	Polymer swelling

Purely diffusional release from a thin film will have n value of 0.5 and Peppas equation will give the Higuchi equation. Values of n that are between diffusion controlled and swelling controlled mechanisms are named as anomalous transport which involves overlapping of different types of phenomena such as drug diffusion and polymer swelling. Again, like Higuchi equation (Eq.2.2), Peppas equation describes a short time approximation of the exact solution of Fick's second law and the short-time approximation is valid for the first 60% of the total released drug ($M_t / M_\infty \leq 0.60$) (Ritger & Peppas, 1987)

There are several other empirical or semi-empirical models that were proposed. For instance, Hopfenberg model proposes a description of drug release from degradable drug

delivery systems with a release rate proportional to the surface area of the excipient. Whereas Cooney model considers surface erosion for spheres and cylinders (J Siepmann & Siepmann, 2008). Hixson and Crowell model recognizes that if the excipient dissolves proportionally in all dimensions, in such dissolution the particle area is proportional to the cubic root of its volume (Costa & Lobo, 2001).

These empirical or semi-empirical models can be very useful to compare different drug release profiles but they may be inadequate for elucidating the underlying mechanisms and the assumptions of each model should be cautiously examined (J Siepmann & Siepmann, 2008).



Chapter 3: Experimental Methods

3.1 Materials

Alginic acid sodium salt (from Sigma Aldrich), CaCl_2 (from Sigma Aldrich, anhydrous, granular) and ethanol (from Isolab) were used for the synthesis of alginate aerogels. Commercial MOFs were used for the composite synthesis. Fe-BTC (Basolite F300) was supplied from Merck (formerly Sigma-Aldrich), ZIF-8 and UiO-66 from ACSYNAM. Paracetamol and ibuprofen (from Merck) were used for drug loading. Phosphate-buffered saline (PBS) tablets were obtained from Amresco (Solon, Ohio).

3.2 MOF/Aerogel Composite Synthesis

Spherical composite aerogel beads with approximately 5 mm diameter were synthesized by combining direct mixing method with dripping technique. Fe-BTC/Ca-Alginate aerogels (Fe-BTC/Alg) with varying Fe-BTC contents (1, 5, 10, 20, 50 and 70%) were synthesized as well as ZIF-8/Ca-Alginate aerogels (ZIF/Alg) with varying ZIF-8 contents (20, 50, 75%) and UiO-66/Ca-Alginate aerogels (UiO/Alg) with varying UiO-66 contents (10, 20, 50, 75%). Also pure calcium alginate (Alg) and zinc alginate (Zn-Alg) beads were synthesized for comparison.

Calcium Alginate is a nontoxic, biocompatible and biodegradable polysaccharide whereas MOFs used in this study are considered to be with appropriate toxicity (Wu & Yang, 2017). Simple mixing method was combined with dripping technique to obtain MOFAC beads as shown in Figure 2.2 (c).

Briefly, 2 wt% sodium alginate aqueous solution was mixed and sonicated with designated MOF amount. The dispersion was then dripped into 0.2 M CaCl_2 solution to induce ionic crosslinking and form an egg-box structure. This way, MOF is entrapped inside the calcium alginate matrix forming a MOF/calcium alginate hydrogel. Next, the hydrogel was subjected to solvent exchange to replace the water inside the pores with ethanol. To reduce the shrinkage of calcium alginate, a step-wise solvent exchange (10, 30, 50, 70, 90, 100 and again 100% ethanol) was performed. MOF/calcium alginate aerogels were then supercritically dried with CO_2 at 313 K and 90 bar using an Applied Separations Speed SFE system with a 26 ml extraction vessel. Prior to placing the synthesized composite gels, the vessel was first filled with some excess amount of solvent enough to cover the beads which was ethanol. This excess solvent was necessary to

prevent the evaporation of solvent from the surface of the alcogel which could lead to shrinkage or cracks on the samples. The vessel was then heated to the extraction temperature and pressurized with CO₂. After reaching thermal equilibrium, the exit valve was opened, the excess solvent was instantaneously removed from the vessel by supercritical CO₂ (scCO₂) and the extraction of ethanol from the pores of the alcogel composites began. The drying of the composite beads took about 2 hours. Then, the vessel was depressurized slowly (around 1 ml/min) in order to avoid formation of a vapor-liquid interface.

Micron sized Fe-BTC/Alg particles were also produced using a modified version of emulsion gelation method explained in the study by Alnaief et al. (Alnaief, Alzaitoun, García-González, & Smirnova, 2011). A suspension of Fe-BTC, sodium alginate and CaCO₃ was dispersed in paraffin oil which contained a surfactant under constant stirring. The formed w/o emulsion was then subject to a small portion of paraffin oil which contained acetic acid. With the addition of acetic acid, the droplets gelled forming micron sized particles trapping Fe-BTC inside the alginate matrix. After removing the oil phase by centrifugation and washing, the gel particles were subjected to solvent exchange with ethanol and dried supercritically. These MOFACs are shown in Figure 3.1.

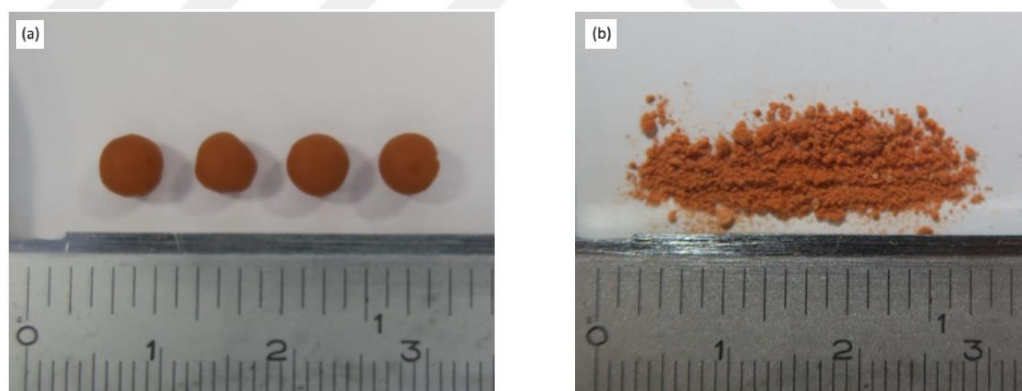


Figure 3.1: Photographs of Fe-BTC/alginate aerogel composites produced via (a) dripping method and (b) emulsion gelation method.

3.3 Drug Loading

The route of encapsulation of molecules in MOFACs' pores depend on the solubility of the molecule in supercritical CO₂. Drugs that are soluble in supercritical CO₂ can be loaded (adsorbed and/or precipitated) from supercritical solutions. However, CO₂ insoluble drugs such as paracetamol are loaded via supercritical antisolvent precipitation process inside the pores.

Supercritical antisolvent precipitation (SAS) is a technique to produce finely comminuted particles (Reverchon, Della Porta, Di Trolio, & Pace, 1998). SAS inside the pores is a loading technique, applicable for compounds that are not soluble in the supercritical medium but soluble in a solvent that is miscible with the supercritical solvent, as explained in detail by Ulker et al (Ulker & Erkey, 2017). Paracetamol being soluble in ethanol but hardly soluble in supercritical CO₂ is therefore incorporated into MOFACs using this method. Encapsulating molecules in MOFACs' pores via SAS process has also not been reported in the literature so far.

Loading from supercritical solutions is a widely used technique to load supercritically soluble drugs into aerogels. During impregnation of ibuprofen using supercritical CO₂, both adsorption on the surface and precipitation inside the pores take place. While the loading amount is related to pore volume and solubility of the drug in scCO₂ in that condition for precipitation, surface area and affinity of the drug molecule to the substrate and the fluid phase are important for adsorption.

3.3.1 Paracetamol Loading via SAS

Paracetamol (PC) is a drug that is highly soluble in ethanol (232.75 g PC/kg ethanol) and water (17.39 g PC/kg water) at 30 °C but poorly soluble in supercritical CO₂ (Granberg & Rasmuson, 1999). This fact enables PC to be loaded on aerogels from the liquid phase during solvent exchange step via SAS process.

Fe-BTC/Alg composites with varying Fe-BTC contents (1,5, 10, 20, 50 and 70%) were loaded with paracetamol as well as ZIF/Alg and UiO/Alg with 20% MOF content. Also pure calcium alginate (Alg) beads were synthesized for comparison.

For PC loading, MOF/Alginate alcogels were placed in PC/ethanol solution at the very last step of solvent exchange. Two different PC/ethanol loading solutions were used: 0.5 M and 1.2 M. Alcogel beads were kept inside these solutions for a day to ensure that paracetamol diffused into ethanol inside the pores. The drug loaded alcogels were then supercritically dried with CO₂ at 40°C and 90 bar as shown on Figure 3.2.

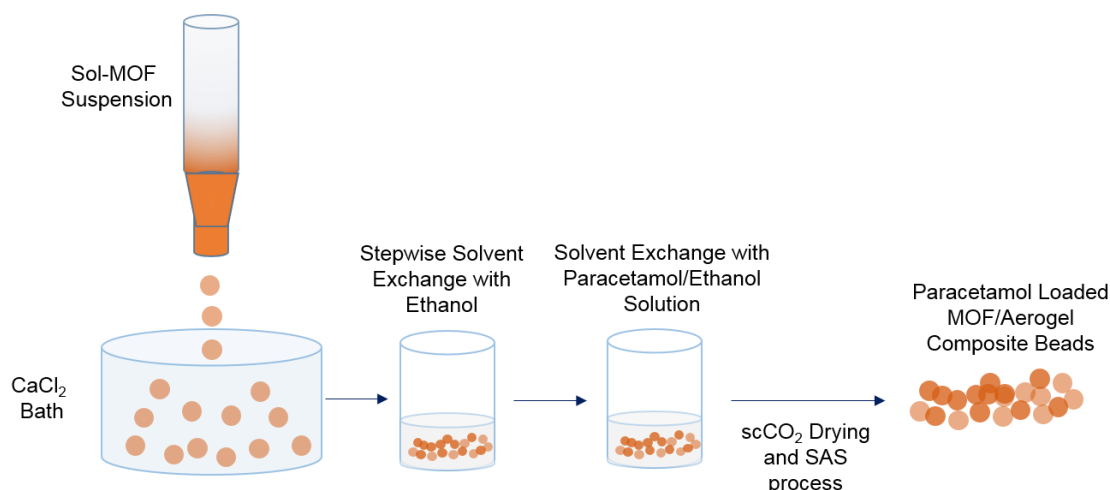


Figure 3.2: Scheme for MOF/aerogel composite production combining simple mixing and dripping method and drug loading with SAS process.

During PC loading on Fe-BTC/alginate alcogels, color change was observed as shown in Figure 3.3. With the diffusion of paracetamol into the pores, orange color of alcogels darkened and changed to purple. This color change can be explained by the weak interaction between the coordinatively unsaturated sites (CUS) of Fe-BTC and secondary amide group of paracetamol. The number of these CUS are very small when compared to the amount of paracetamol present inside the pores and the weakness of the interaction allows this color change to be reversible. The orange color is obtained back during the release process as shown in Figure 3.4. No color change was observed for ZIF/Alg or UiO/Alg composites both during loading and delivery.



Figure 3.3: Color change of Fe-BTC/Alginate alcogels during paracetamol loading.

After the diffusion of PC into the pores, two different strategies were used in drying. In one of them, the beads were removed from the PC loading solution and placed immediately in the extraction vessel without any excess solution. The vessel was then sealed and charged with scCO₂. In the second strategy, the beads together with the PC loading solution was placed in the extraction vessel. PC/ethanol solution was used instead of pure ethanol as excess solvent in order to prevent diffusion of the drug out of the composite beads due to a concentration gradient. The vessel was then sealed and charged

with scCO₂. The former ones were denoted as no excess whereas the latter were denoted as excess. The effect of this difference was investigated in terms of loading amounts and delivery rates.

The alcogels were then subjected to scCO₂ at 313 K and 90 bar which led to removal of the ethanol from the pores and supercritical antisolvent precipitation (SAS) of paracetamol inside the pores. ScCO₂ charged into the vessel first dissolved in ethanol inside the pores leading to volumetric expansion of the PC/ethanol solution. As more CO₂ dissolved, the PC/ethanol solution first became supersaturated and then paracetamol began to precipitate inside the pores. The extraction was continued until no ethanol was left inside the pores. A small amount of paracetamol was also extracted during this process while most of it precipitated inside the pores and on the outer surface of the composite beads.

Drug loading was calculated by Equation 3.1:

$$\text{Drug Loading (wt\%)} = \frac{m_{\text{drug}}}{m_{\text{drug-MOFAC}}} \times 100 \quad (3.1)$$

$$\text{where } m_{\text{drug}} = m_{\text{drug-MOFAC}} - m_{\text{MOFAC}} \quad (3.2)$$

Here m_{drug} is the weight of paracetamol (or ibuprofen) in mg, $m_{\text{drug-MOFAC}}$ is the weight of drug loaded composite and m_{MOFAC} is the weight of the composite without loaded drug. 15 different beads were weighed and averaged for this calculation. The weight of PC m_{PC} obtained through weighing was also expected at the end of delivery and a mass balance closure was done by comparing this value with the theoretical (expected) loading of PC:

$$\text{expected drug (mg)} = V_{\text{beads}} \times \varepsilon \times C_{\text{PC in EtOH}} \times MW_{\text{PC}} \quad (3.3)$$

where $C_{\text{PC in EtOH}}$ is the molar concentration of the initial loading solution $\frac{\text{moles}}{\text{L}}$.



Figure 3.4: Fe-BTC/Alginates changing back to original color during release process.

3.3.2 Ibuprofen loading from scCO₂

The drug ibuprofen (IBU) was loaded on MOF/Aerogel composites through

adsorption from supercritical solutions as a post treatment. ZIF/Algs with varying ZIF-8 content (20, 50, 75%), also 50% ZIF/Zn-Alg were loaded with ibuprofen. Moreover, UiO/Algs with varying UiO-66 content (10, 20, 50, 75%) were loaded with ibuprofen. Calcium Alginate (Alg) and Zinc Alginate (Zn-Alg) are also loaded with ibuprofen for comparison. Ibuprofen drug molecule is highly hydrophobic, poorly water soluble has dimensions of $4.3 \times 5.0 \times 11.0 \text{ \AA}^3$.

Loading conditions of ibuprofen used in this study are 3300 psi (227 bar) and 40°C. Solubility of ibuprofen in scCO₂ around this condition was 6.49×10^{-3} (mole fraction) at 220 bar (3190 psi) and 40°C (Charoenchaitrakool, Dehghani, Foster, & Chan, 2000). Generally, 30 mg IBU and 75 mg MOFAC was placed inside the custom-made 54 ml high-pressure stainless-steel vessel. The vessel was then heated to 40°C, pressurized with CO₂ to 3300 psi and kept at these conditions for 24 h. After dissolution and adsorption of ibuprofen, the vessel was depressurized slowly at 40°C. The drug loading was determined gravimetrically.

It is important to note that supercritical activation of MOFACs before drug loading is essential. Therefore prior to drug loading, MOFACs were supercritically activated in 26 ml supercritical extraction vessel using Applied Separations SFE system at 90 bar and 40°C. Loading was determined gravimetrically.

3.3.3 *Ibuprofen loading from water*

Ibuprofen adsorption on the synthesized composites from water were studied at 37°C under constant stirring in oven. 200 µL samples were taken at specific time points from the fluid phase and same amount of distilled water was added to keep the total volume constant. The samples taken were analyzed by Agilent 1200 HPLC using 60% acetonitrile and 40% water as mobile phase. The flow rate was adjusted to be 2 ml/min and Agilent XDB -C18 column was used. The UV lamp of detector was set to 224 nm. The injection volume was 50 µL each time and at least 3 data were taken and averaged.

3.4 Drug Release Studies

3.4.1 *Paracetamol Release*

For paracetamol delivery studies, one PC loaded composite bead was placed in 30 ml of medium which is phosphate buffered saline (PBS) at pH 5.8 or water at neutral pH at 310 K and under constant stirring to avoid external diffusion process. Samples of 100 µl were taken from the release medium at specific time points and same amount of fresh

medium was added to keep the total volume constant throughout the delivery.

The samples taken were analyzed by Nanodrop 1000 UV-spectrophotometer at wavelength 244 nm. Preparing calibration curves for PC in both PBS and water at 244 nm at a concentration range between 0.011-0.11 mg/ml, the concentration of PC in the release medium was estimated. The percent releases were calculated using the equation:

$$\% \text{ release} = \frac{C_{drug} V_{sol}}{m_{drug}} \times 100 \quad (3.4)$$

where C_{drug} is the concentration of the drug at the release medium at a given time, V_{sol} is the volume of the release medium and m_{drug} is the amount of drug loading.

3.4.2 Ibuprofen Release

For ibuprofen delivery studies, 10 beads of composite synthesized were placed in 1000 g of distilled water at neutral pH and 310 K under stirring. Poor solubility of ibuprofen in water required large volume of water to attain the sink conditions. Samples of 400 μ l were taken from the release medium at specific time points and same amount of fresh medium was added to keep the total volume constant throughout the delivery.

The samples taken at specific time points were analyzed by Agilent 1200 HPLC using 60% acetonitrile and 40% water as mobile phase. The flow rate was adjusted to be 2 ml/min and Agilent XDB -C18 column was used. The UV lamp of detector was set to 230 nm. The injection volume was 50 μ L each time. A calibration curve was prepared at these conditions for ibuprofen concentrations between 0.003 to 0.0089 mg/ml in water. The concentration of ibuprofen in release medium was estimated with this calibration curve. The percent releases were calculated using Equation 3.4.

3.5 Characterization Techniques

The obtained MOFAC beads had 4 mm diameter on average which were measured using a caliper. The weight percent of MOF was found by simply taking the ratio of the amount of MOF added to the mass of sodium alginate used in the initial solution. The density of the samples (ρ_{bulk}) was determined simply by dividing the final mass of the composites by their final volume. Bead porosities were calculated as follows:

$$\varepsilon = 1 - \frac{\rho_{bulk}}{\rho_{skeletal}} \quad (3.5)$$

Skeletal densities of MOFACs were calculated as in Equation 3.6:

$$\rho_{skeletal} = \rho_{MOF} w_{MOF} + \rho_{Alg} w_{Alg} \quad (3.6)$$

Using a pycnometer, skeletal density of pure alginate was found to be 1.85 g/cm³. Skeletal density of pure Fe-BTC was found to be 1.677 g/cm³ by Ploegmakers et al. (Ploegmakers, Japip, & Nijmeijer, 2013), for ZIF-8 it was found to be 1.4 g/cm³ by Bose et al. (Bose et al., 2020) and for UiO-66 it was found to be 1.65 g/cm³ by Bambalaza et al (Bambalaza et al., 2018).

Pore volume per mass of aerogel, V_p , was also calculated using Equation 3.7:

$$V_p = \frac{1}{\rho_{bulk}} - \frac{1}{\rho_{skeletal}} \quad (3.7)$$

Pore structure of the composite materials was analyzed with Zeiss Ultra Plus Field Emission Scanning Electron Microscope. Samples were first coated with gold to prevent charging.

Pore properties such as pore size, pore volume, Brunauer, Emmett and Teller (BET) surface area and t-plot micropore area of the samples were characterized using N₂ physisorption using a Micromeritics ASAP 2020 instrument. The samples were primarily degassed at 333 K under vacuum for 24 hours prior to analysis. XRD measurements were carried out on a Bruker D8 Advance Diffractometer (Cu-K α ; 1.54018 Å) in a range of 5° to 55°. IR spectra were recorded using Attenuated Total Reflectance (ATR) spectroscopy Thermoscientific Nicolet IS10 spectrophotometer. For analysis, cross-sections of composites were used. The resolution was set at 4 cm⁻¹ by averaging 64 scans in Mid IR region of 4000–650 cm⁻¹.

Chapter 4: Results and Discussion

4.1 Characterization of MOFACs

4.1.1 Physical Characterization

The physical properties of the synthesized aerogels are shown in Table 4.1. With increasing MOF content, bulk densities of composites increased, porosities and pore volumes of the composites decreased approaching pure MOF's physical properties. For composites with 20% MOF loading, Fe-BTC/Alg and UiO/Alg composites show similar behavior whereas ZIF/Alg composite has lower density, higher porosity and higher pore volume. This is due to the fact that hydrophobic ZIF-8 prevented the moisture and shrinkage of matrix caused by the moisture. Although not quantified, there was an increase in mechanical strength of the composites as MOF content increased.

Table 4.1: Physical properties of the synthesized composites

Sample	Density (g/cm ³)	Porosity (ϵ)	V _p (cm ³ /g)
Calcium Alginate	0.0456	0.975	21.39
1% Fe-BTC/Ca-Alginate	0.050	0.973	19.46
5% Fe-BTC/Ca-Alginate	0.0515	0.972	18.88
10% Fe-BTC/Ca-Alginate	0.0527	0.971	18.44
20% Fe-BTC/Ca-Alginate	0.0616	0.966	15.69
50% Fe-BTC/Ca-Alginate	0.082	0.953	11.62
70% Fe-BTC/Ca-Alginate	0.135	0.922	6.79
20% ZIF-8/Ca-Alginate	0.042	0.976	23.24
20% UiO-66/Ca-Alginate	0.060	0.967	16.11

SEM images shown in Figure 4.1 show the external and internal surfaces of paracetamol loaded composites with low MOF content (5%) and high MOF content (70%). Paracetamol crystals and precipitates were observable on both composites' external surfaces. Fe-BTC aggregates were more visible and frequent at 70% Fe-BTC/Alg as expected. Paracetamol was not in crystal form inside the pores but rather as precipitate and its presence was validated with cross-sectional FTIR analysis.

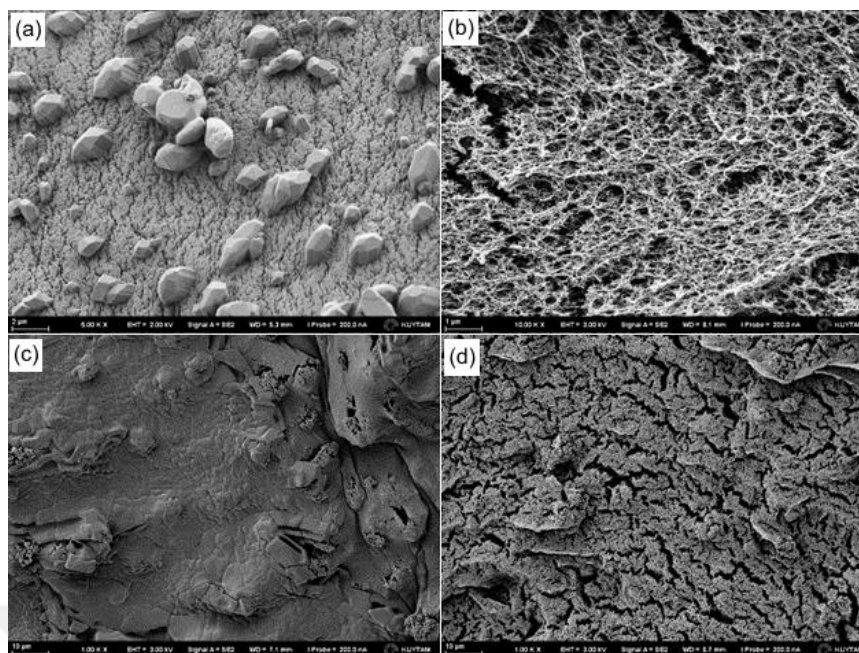


Figure 4.1: SEM images of external and internal surfaces of PC loaded 5% Fe-BTC/Alg aerogels (a, b), 70% Fe-BTC/Ca-Alginate aerogels (c,d).

4.1.2 XRD Results

XRD spectra shown in Figure 4.2 indicated weak and broad peaks of Fe-BTC and were observed in a range of 5–50° revealing low crystallinity due to the semi-amorphous nature of Fe-BTC. 1% Fe-BTC/Alg shows no distinct peaks of Fe-BTC but rather the broad hump which is the characteristic of calcium alginate. However, 70% Fe-BTC/Alg showed the exact peaks of Fe-BTC with high intensities with an addition of a small peak that corresponds to alginate hump at around 15°.

XRD data of drug loaded Fe-BTC/Alg composites are shown in Figure 4.3. Sharp and distinct peaks that are characteristic of paracetamol indicated the crystallinity of the drug on the external surface regardless of the composite. While the broad peaks of Fe-BTC cannot be seen in 1% and 5% Fe-BTC/Alg composites, they are clearly observed along with PC peaks in 70% Fe-BTC/Alg.

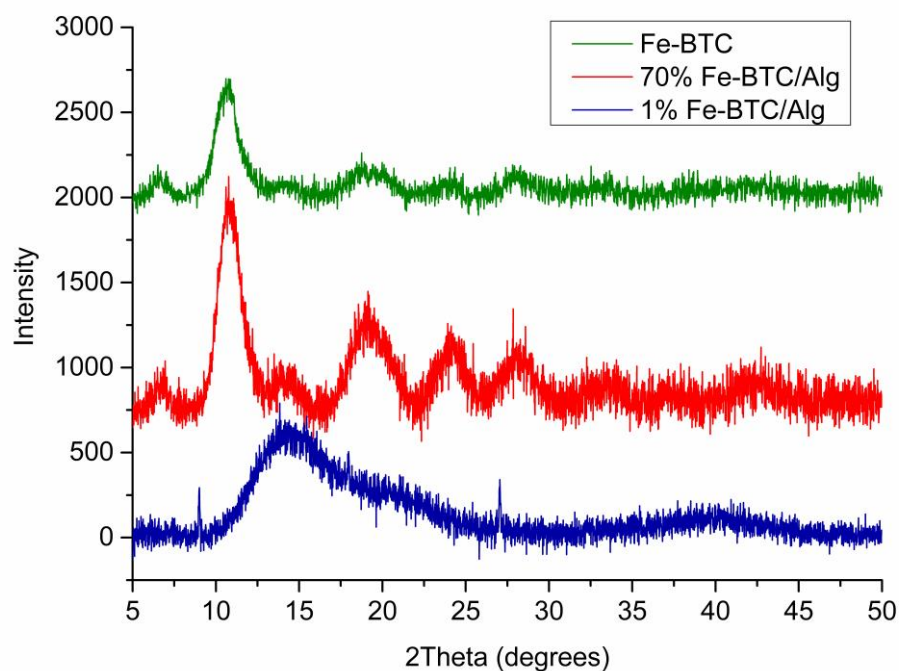


Figure 4.2: XRD spectra of pristine Fe-BTC, 1% Fe-BTC/Alg and 70% Fe-BTC/Alg.

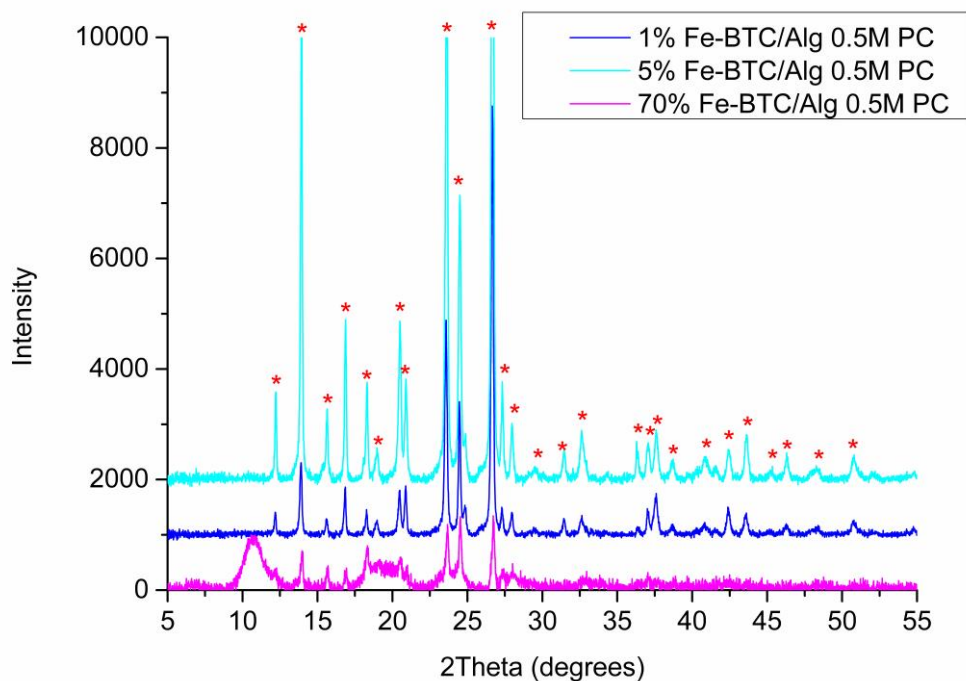


Figure 4.3: XRD spectra of different Fe-BTC/Alg composites loaded with paracetamol.

*refers to Paracetamol PDF 00-065-1377.

XRD spectra of 20% ZIF-8/Alg and 20%UiO-66/Alg are provided in Figure 4.4

and Figure 4.5. All the characteristic peaks of ZIF-8 was clearly observable on the composites but with a decreased intensity in paracetamol loaded one. Paracetamol was again in crystalline form on the external surfaces of the drug loaded composite. On the XRD spectra of 20% UiO-66/Alg, although all the characteristic peaks of paracetamol and UiO-66 were observable in the paracetamol loaded composite's spectra, only the high intensity peaks of UiO-66 were observed in the unloaded composite.

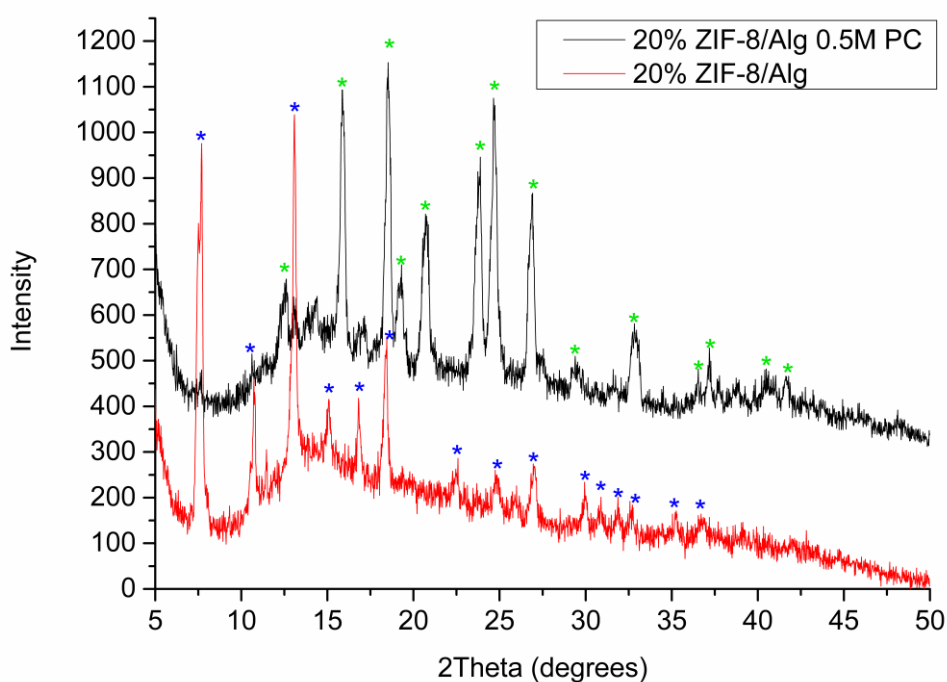


Figure 4.4: XRD spectra of 20% ZIF-8/Alg aerogel with and without paracetamol.

* refers to Paracetamol PDF 00-065-1377 and * refers to ZIF-8 PDF 00-062-1030

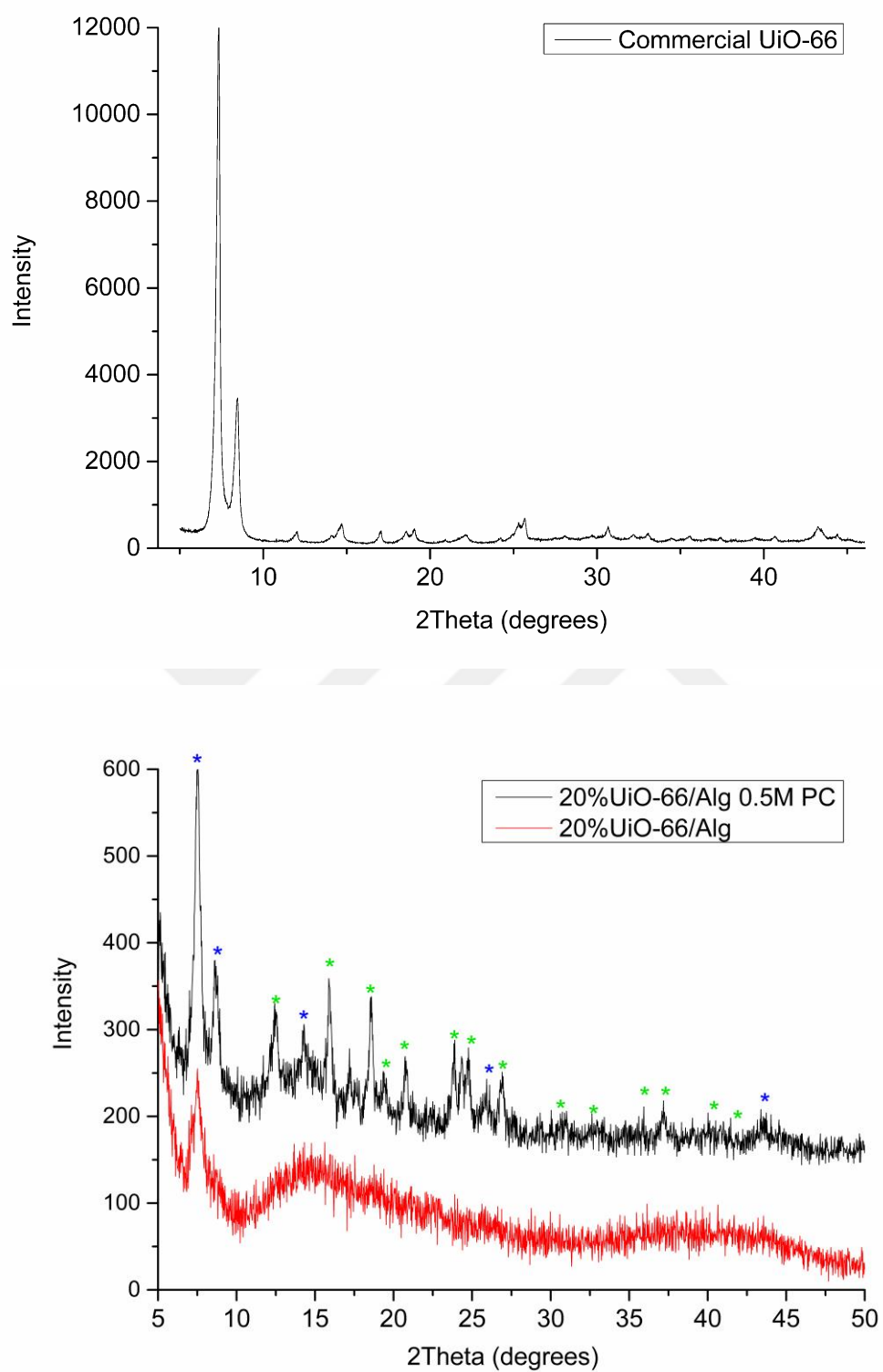


Figure 4.5: XRD spectra of pristine UiO-66 and 20% UiO-66/Alginate aerogel with and without paracetamol. * refers to Paracetamol PDF 00-065-1377

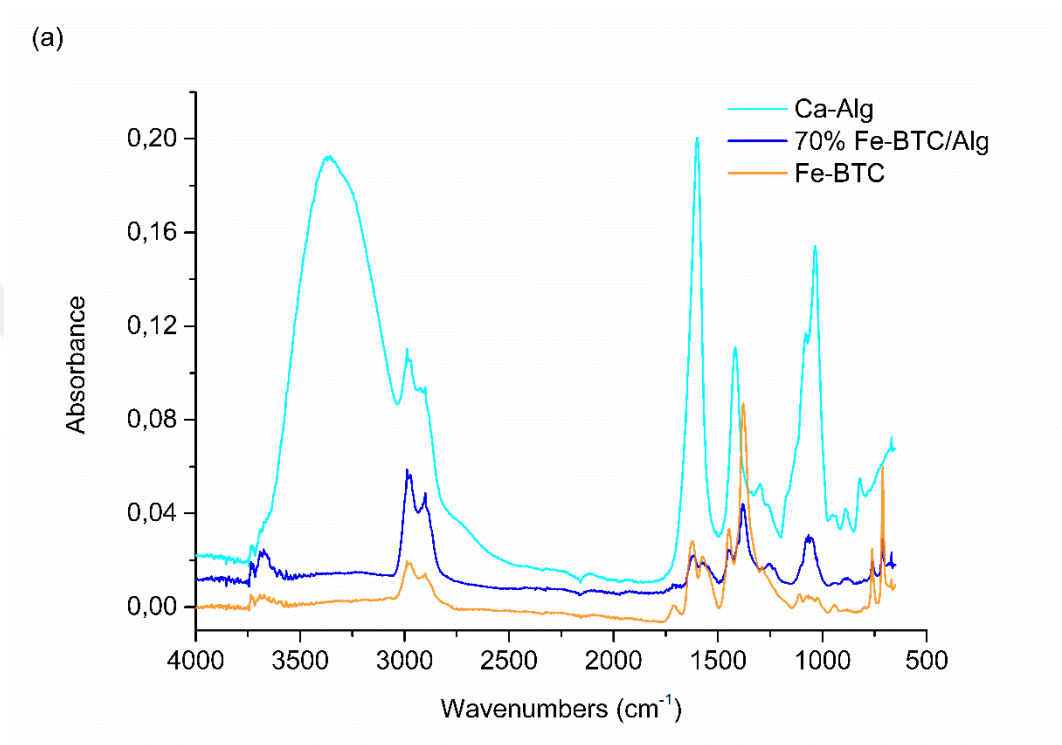
4.1.3 IR Spectra Results

In the FTIR spectrum shown in Figure 4.6a, peaks at 1710, 1622, 1572, 1447, and 1380 cm^{-1} which were attributed to metallic esters of Fe-BTC and peaks at 940, 761, and 712 cm^{-1} which were associated with organic linker's C-CO₂ bond were all observable in Fe-BTC/Alg composite (Akarçay, Kurtoğlu, & Uzun, 2020). The characteristic asymmetric and symmetric stretching vibrations of carboxylate groups that are coordinated to Ca²⁺ ions at 1602 and 1418 cm^{-1} in calcium alginate's spectrum were present in Fe-BTC/Alg as well as their corresponding stretching vibrations at 1081 and 1034 cm^{-1} that belong to C-O-C groups on the sugar ring (Paraskevopoulou et al., 2020). Aliphatic C-H stretching vibrations observed between 2900 and 3000 cm^{-1} were present in 70% Fe-BTC/Alg. For calcium alginate, the stretching vibrations of O-H bonds at 3300 cm^{-1} showed a strong and broad peak which disappeared in 70% Fe-BTC/Alg due to loss of moisture in scCO₂ activated composite. Alginate peaks present at 1300, 890 and 820 cm^{-1} were also present in Fe-BTC/Alg. This suggests that Fe-BTC and alginate formed a physical mixture in the composite.

To gain insight on paracetamol presence and understand the interaction of the drug with the composite, cross-sections of composites were used and shown on Figure 4.6b. Paracetamol characteristic vibrational peaks for N-H at 3320 cm^{-1} , a broad CH₃ stretching between 3160 and 3035 cm^{-1} were present in PC and PC loaded composite spectra (Burgina, Baltakhinov, Boldyreva, & Shakhtschneider, 2004; Trivedi, Patil, Shettigar, Bairwa, & Jana, 2015). The asymmetrical bending of C-H bond at 1503 cm^{-1} and C-H bending at 1434 cm^{-1} were observed in both PC and PC loaded composite. C-NH stretching at 1171 cm^{-1} and phenol O-H bending at 1368 cm^{-1} were observed in both PC and PC loaded composite. C=O stretching of PC at 1650 cm^{-1} was also present in PC loaded composite and aromatic C=C stretching of PC at 1610 cm^{-1} was observable in both PC and PC loaded composite. C-N amide stretching was observed at 1107 cm^{-1} in both PC and PC loaded composite. However, the N-H stretching vibrations of PC at 3320 cm^{-1} had shifted to 3323 cm^{-1} for the PC loaded composite. The N-H bending peak appeared at 1561 cm^{-1} in PC appeared at 1564 cm^{-1} in PC loaded composite. Aromatic amine C-N stretching was present at 1326 cm^{-1} in PC shifted to 1328 cm^{-1} in PC loaded composite. These small shifts to higher wavenumbers suggest that paracetamol is interacting with the composite with its secondary amide group.

On the other hand, peaks of metallic esters of Fe-BTC at 1447 cm^{-1} and 1380 cm^{-1}

in the composite has shifted to a lower wavenumbers of 1443 cm^{-1} and 1377 cm^{-1} in PC loaded composite. It can be explained as a weak complex formation between the coordinatively unsaturated sites (CUS) of Fe-BTC and secondary amide group of paracetamol. This showed a weak interaction between the paracetamol and Fe-BTC/Alg composite which was probably responsible for the color change during loading and delivery.



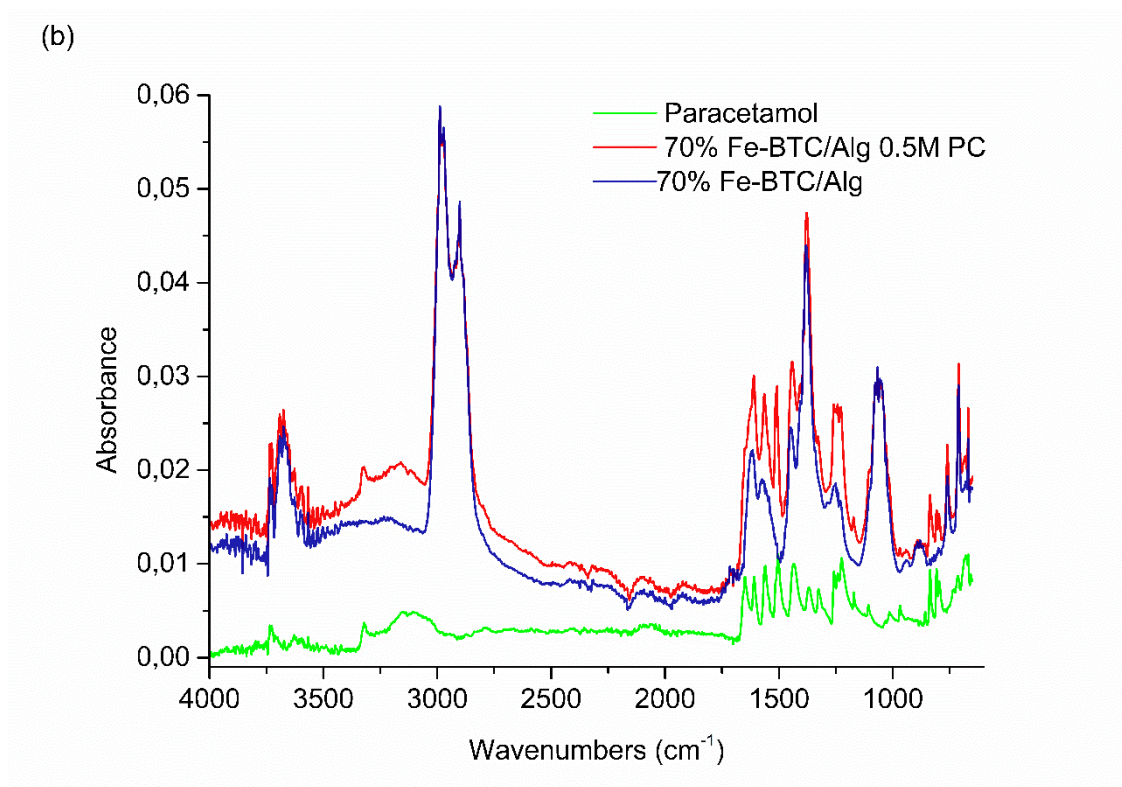


Figure 4.6: FTIR spectra of native Fe-BTC, Ca-Alginate, their composite (a) and its interaction with the drug paracetamol (b)

4.1.4 BET Results

The macro-, mesoporous nature of calcium alginates were already studied and present in the literature (Gurikov, Raman, Weinrich, Fricke, & Smirnova, 2015; M. Robitzer et al., 2011; Mike Robitzer et al., 2008; Mike Robitzer, Renzo, & Quignard, 2011). Our nitrogen adsorption study on calcium alginate is in line with these findings. While the hysteresis loop at relatively high pressures is a typical type IV isotherm which indicates presence of mesopores (pores with diameter between 2 nm and 50 nm), the final rise of the isotherm at relative pressure around $p/p^0=0.99$ indicates presence of macropores with pore diameter more than 50 nm. This also explains the discrepancy between the pore volumes calculated by the difference in reciprocals of bulk and skeletal density as in Equation 3 and the BJH pore volume found with N_2 physisorption (Şahin, Uzunlar, & Erkey, 2019). Table 4.2 and Figure 4.7 show the results of the N_2 adsorption analysis performed for the composites. BET surface area of the composites increased with increasing weight fraction of the MOF Fe-BTC despite of some discrepancies caused by shrinkage of calcium alginate observable at low weight fractions of MOF presence.

Negligible microporosity of calcium alginate was altered by the addition of microporous MOFs and the microporosity was distinguished from mesopores via t-plot method. T-plot micropore area was found to increase almost proportionally to the weight fraction of the MOFs seen in Figure 4.8. This means that the alginate that surrounds the MOF particles did not clog MOFs micropores and therefore MOFs micropores were open and accessible. BJH pore volume had a decreasing trend with increasing MOF weight fraction. This is due to loss of mesopores in the alginate aerogel since they're being replaced by microporous MOFs. However, discrepancies were present and BJH pore volumes are unreliable for these systems due to high macroporous volumes present within the alginate aerogel.

Table 4.2: Nitrogen adsorption analysis of the composites

Sample	w_{MOF}	BET surface area (m^2/g)	t-Plot micropore area (m^2/g)	t-Plot micropore volume (cm^3/g)	BJH Pore Volume (cm^3/g)	Ref
Calcium Alginate	0	236.77	52.25	0.022	0.58	(Şahin,2019)
5% Fe-BTC/Ca-Alginate	0.05	434.4	101.6	0.04	0.71	
10% Fe-BTC/Ca-Alginate	0.1	422.19	122.94	0.054	0.57	
20% Fe-BTC/Ca-Alginate	0.2	629.2	158.2	0.07	0.83	
50% Fe-BTC/Ca-Alginate	0.5	738.7	381.6	0.17	0.60	
70% Fe-BTC/Ca-Alginate	0.7	754.6	467.3	0.21	0.41	
Fe-BTC	1	859	796		0.38	(Sanchez,2015)
20% ZIF-8/Ca-Alginate	0.2	444.4	154.7	0.07	1.8	

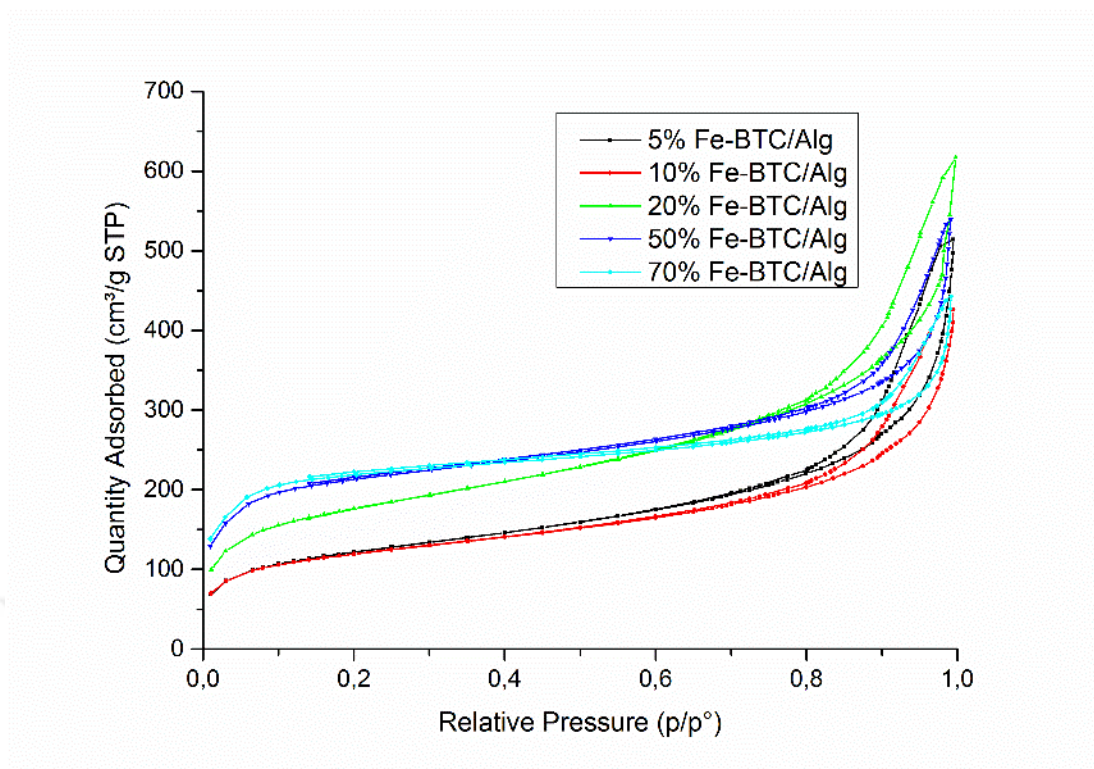


Figure 4.7: N_2 adsorption isotherms of Fe-BTC/Alginate composites.

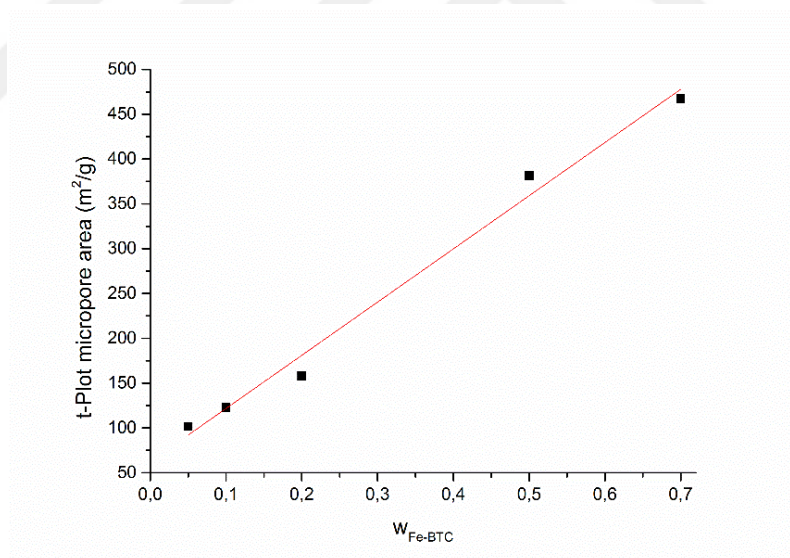


Figure 4.8: The relation between t-plot micropore area and weight fraction of Fe-BTC present in composites.

4.2 Drug Loading: Paracetamol

4.2.1 Effect of Loading Solutions

The composite materials were loaded with paracetamol from ethanolic solutions. The effect of initial PC/ethanol loading solutions on drug loadings were assessed. Two different concentrations of loading solution were used: 0.5 M and 1.2 M as an upper limit due to the fact that 1.2 M is almost saturation of PC in ethanol (Granberg & Rasmuson, 1999). The drug loadings were summarized in Table 4.3. PC loadings clearly increased as the initial concentrations of PC ethanolic solutions increased.

Table 4.3: Effect of initial loading solution on drug loadings

Sample	Paracetamol Loading (wt %)	
	Initial PC	Initial PC
	Concentration: 0.5M	Concentration: 1.2 M
20% Fe-BTC /Ca-Alg	48.5	69.5
20% ZIF-8 /Ca-Alg	49.7	62

4.2.2 Effect of Excess Solution

During SAS process, placing pure excess solvent inside the vessel was avoided to prevent the loaded drug from diffusing out of the pores. In this study, the presence of excess PC/ethanol solution at a same concentration of the loading solution was investigated and compared with totally avoiding excess. The effect of having excess PC/ethanol solution on drug loadings and release profiles were studied. The increase in loadings of the drug was clearly observable when there was excess solution during supercritical drying and shown in Table 4.4.

Table 4.4: Effect of having an excess PC-ethanol solution

Sample	Paracetamol Loading (wt%)	
	No Excess	Excess
20%UiO-66 /Ca-Alg	30.7	45.3
20% Fe-BTC /Ca-Alg	48.5	62
Ca-Alg	62.7	70.1

4.3 Drug Loading: Ibuprofen

4.3.1 Loading from $scCO_2$

As ibuprofen is soluble in $scCO_2$, it was loaded on the composites from supercritical solutions as a post treatment. During this process, both adsorption on the surface and precipitation inside the pores take place. Therefore, loading amount is related to pore volume and solubility of the drug in $scCO_2$ in that condition (precipitation part), surface area, affinity of the drug molecule to the substrate and the fluid phase (adsorption part).

30 mg of ibuprofen was placed inside the vessel for each loading. High amounts were avoided to prevent blockage at the outlet and melting point depression which resulted in shrinkage of the composites. For all loadings, 75 mg MOFAC was placed inside the vessel. The vessel was then heated to 40°C, pressurized with CO_2 to 3300 psi and kept for 24 h. Ibuprofen loadings of the composites under these conditions are given in Table 4.5. Generally, aerogel literature uses wt% ($\text{mg IBU}/(\text{mg IBU} + \text{mg MOFAC}) \times 100\%$) whereas MOF literature uses mg IBU/mg MOFAC. For this reason, both were calculated and provided in Table 4.5. The comparison of composite loadings with literature are also provided in Appendix A.

Table 4.5: Ibuprofen Loadings of MOFACs from supercritical CO_2

Samples	mg IBU/ mg MOFAC	mg IBU/ (mg IBU+ mg MOFAC)
IBU@Calcium Alginate	0.317	0.241
IBU@ 10% UiO-66/Calcium Alginate	0.232	0.189
IBU@ 20% UiO-66/Calcium Alginate	0.211	0.174
IBU@ 20% UiO-66/Calcium Alginate	0.203	0.169
IBU@ 50% UiO-66/Calcium Alginate	0.256	0.204
IBU@ 50% UiO-66/Calcium Alginate	0.318	0.242
IBU@ 75% UiO-66/Calcium Alginate	0.216	0.177
IBU@ 75% UiO-66/Calcium Alginate	0.229	0.186
IBU@ 75% UiO-66/Calcium Alginate	0.285	0.222
IBU@ 20% ZIF-8/Calcium Alginate	0.237	0.191
IBU@ 50%ZIF-8/Zinc Alginate	0.267	0.211
IBU@ 50%ZIF-8/Calcium Alginate	0.325	0.245
IBU@ 75%ZIF-8/Calcium Alginate	0.302	0.232

The amount of MOF (UiO or ZIF) inside the composites did not make a big effect on ibuprofen loading. With increasing MOF content inside the composites, there was definitely more drug per bead but as the density of the composite increased as well, no effect was observed in terms of drug loading wt%. When different MOFs were compared keeping MOF amounts constant, no big differences were seen either. Ibuprofen was not expected to adsorb inside the pores of ZIF-8 due to the fact that the pore apertures are smaller than an ibuprofen molecule but UiO-66 pore apertures are big enough to enable ibuprofen adsorption inside the pores. This might be due to the adsorption kinetics of ibuprofen on these MOFs in scCO₂. Comparing calcium and zinc to crosslink alginate, calcium crosslinked ones had slightly higher loadings than zinc crosslinked ones. Same was valid for 50%ZIF/Ca-Alg when compared to 50%ZIF/Zn-Alg although the difference was less with the presence of ZIF-8 inside the composites.

From the drug loaded (m_{uptake}) and the solubility of ibuprofen in CO₂ under the loading conditions, the amount of ibuprofen that was adsorbed ($m_{adsorbed}$) and that precipitated (m_{ppt}) were calculated using the equation:

$$m_{uptake} = m_{ppt} + m_{adsorbed} \quad (4.1)$$

The calculations showed that less than 1 mg of ibuprofen could precipitate inside the pores whereas at least 20 mg of the drug was adsorbed on the composites.

Assuming a linear adsorption isotherm for calcium alginate, the following graph could be constructed for alginate aerogel:

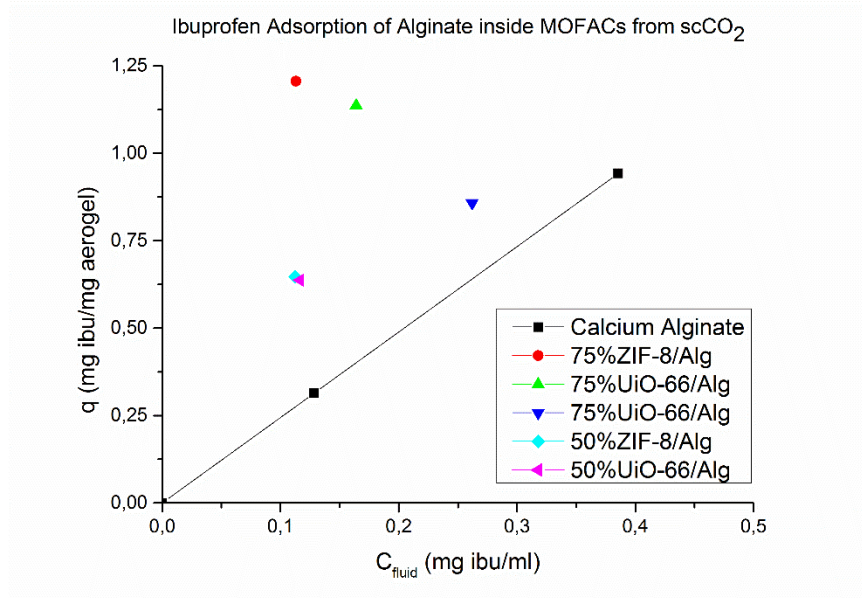


Figure 4.9: Ibuprofen Adsorption Isotherm of Alginate from scCO₂ at 227 bar and 40°C.

50% and 75% UiO-66 or ZIF-8 loaded MOFACs clearly show higher affinity to ibuprofen than calcium alginate. From this data, the adsorption of MOFs inside the MOFACs were calculated and the following graphs were constructed as shown on Figure 4.10.

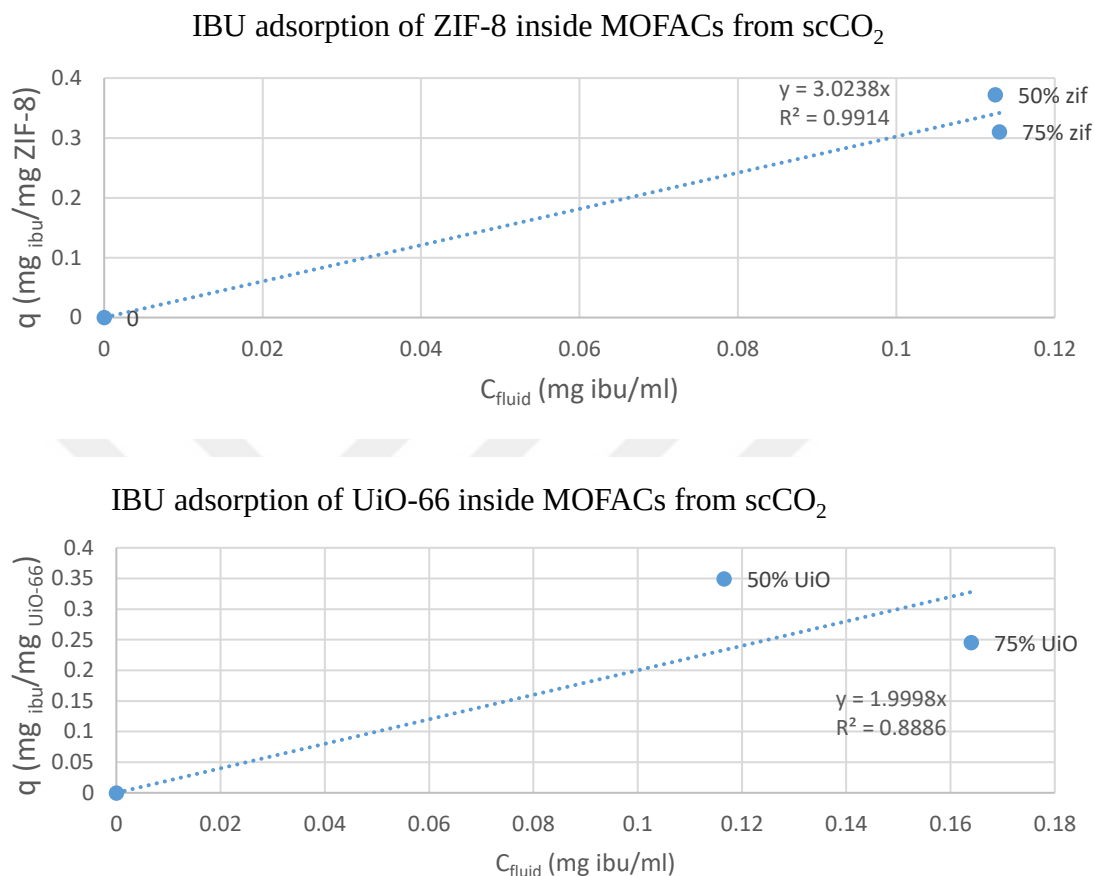


Figure 4.10: IBU adsorption of ZIF-8 and UiO-66 inside MOFACs from scCO₂

4.3.2 Loading from water

In addition to adsorption from scCO₂, adsorption of ibuprofen from water at 37°C was also studied to gain insight about the affinity of the drug to release medium and understand the release kinetics. For this study, calcium alginate, zinc alginate, UiO-66/Alg MOFACs with 50 and 75% MOF content were used as well as pristine UiO-66 in pellet form.

Calcium and zinc alginates showed very little affinity with almost no uptake of ibuprofen from water. For 50% UiO/Alg and 75%UiO/Alg, ibuprofen uptake was present and shown in Figure 4.11. Since no adsorption was observed for alginate, ibuprofen uptakes were calculated on UiO amount inside the designated composites.

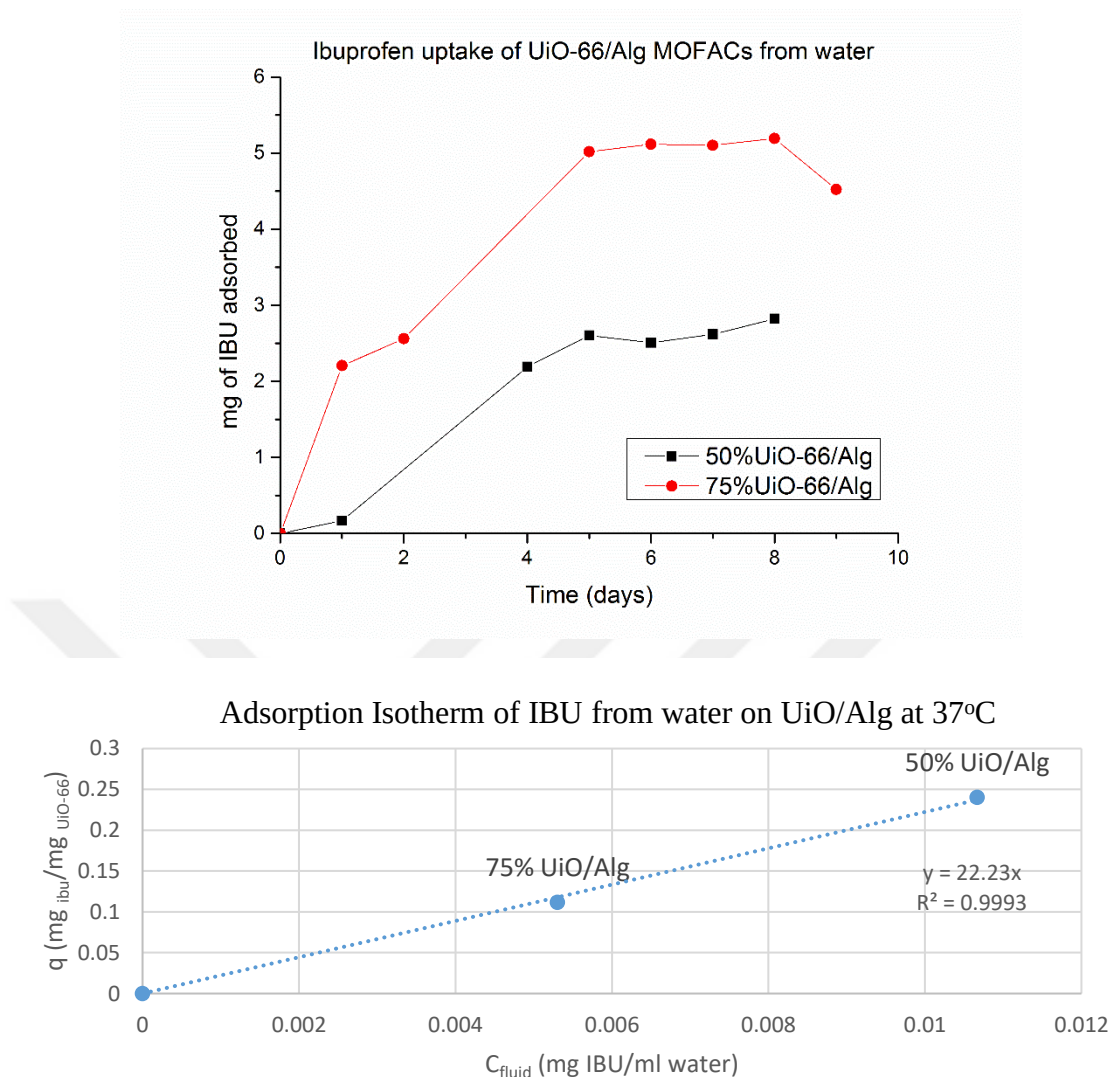


Figure 4.11: Ibuprofen adsorption of 50% and 75% UiO-66/Algs from water at 37°C.

Ibuprofen adsorption on UiO-66 pellets from water was also studied. 3 uptake experiments at different initial concentrations of 11.1, 15.4 and 20.8 mg/L ibuprofen in water were performed. The ibuprofen uptake took 20 days. The adsorption kinetics and adsorption isotherm of UiO-66 pellets were shown in Figure 4.12.

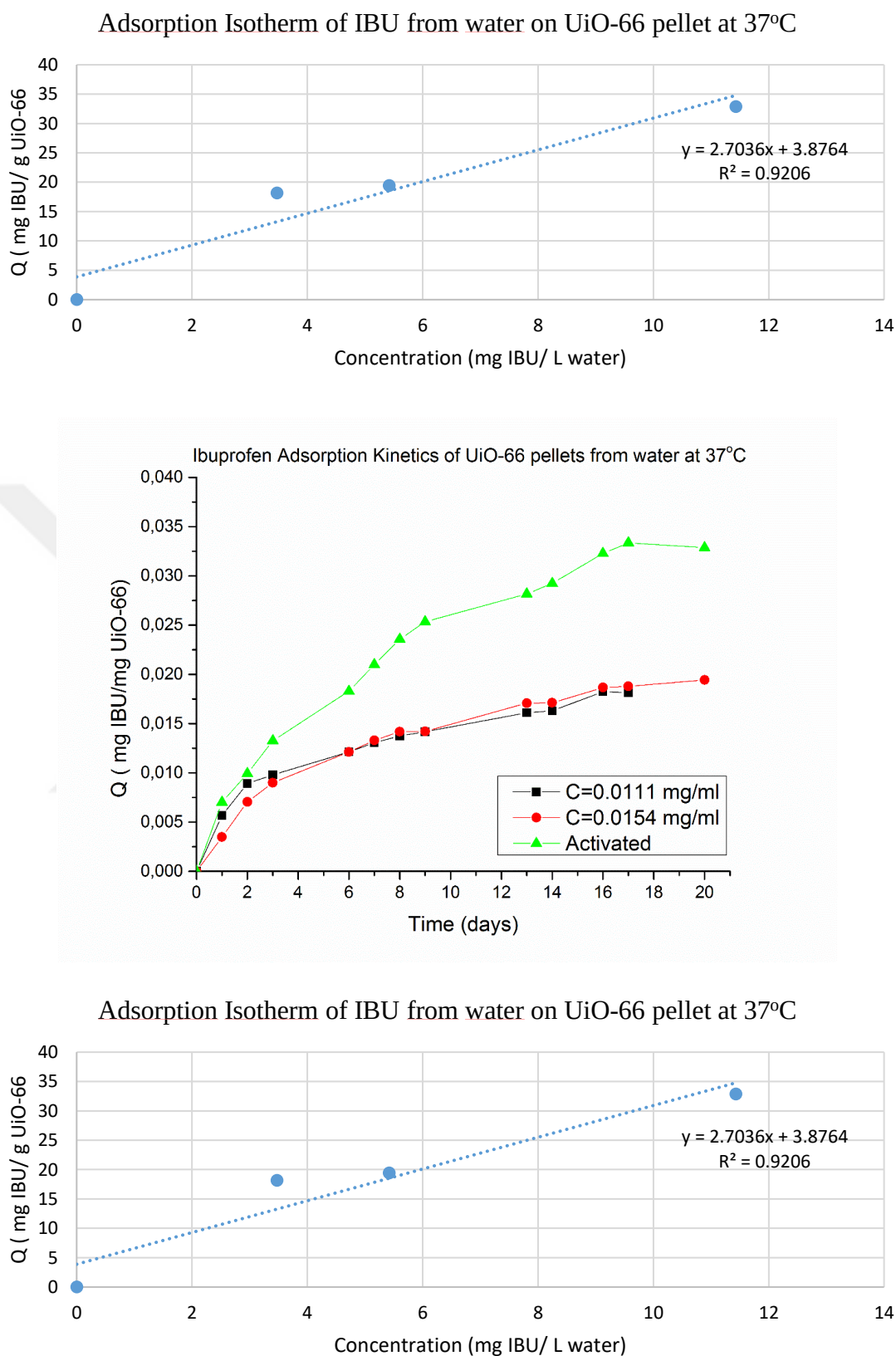


Figure 4.12: Adsorption kinetics and adsorption isotherm of UiO-66 pellets from water at 37°C

The adsorption kinetics of UiO-66 pellets were also fitted to kinetic models. The best fits were pseudo-second-order kinetic model for initial ibuprofen concentrations 0.0111 mg/ml and 0.0154 mg/ml whereas pseudo-first-order kinetic model for initial ibuprofen concentration 0.0208 mg/ml and they are given in Figure 4.13. They also fitted to the Higuchi equation well with $R^2 > 0.97$, meaning they are purely diffusion controlled.

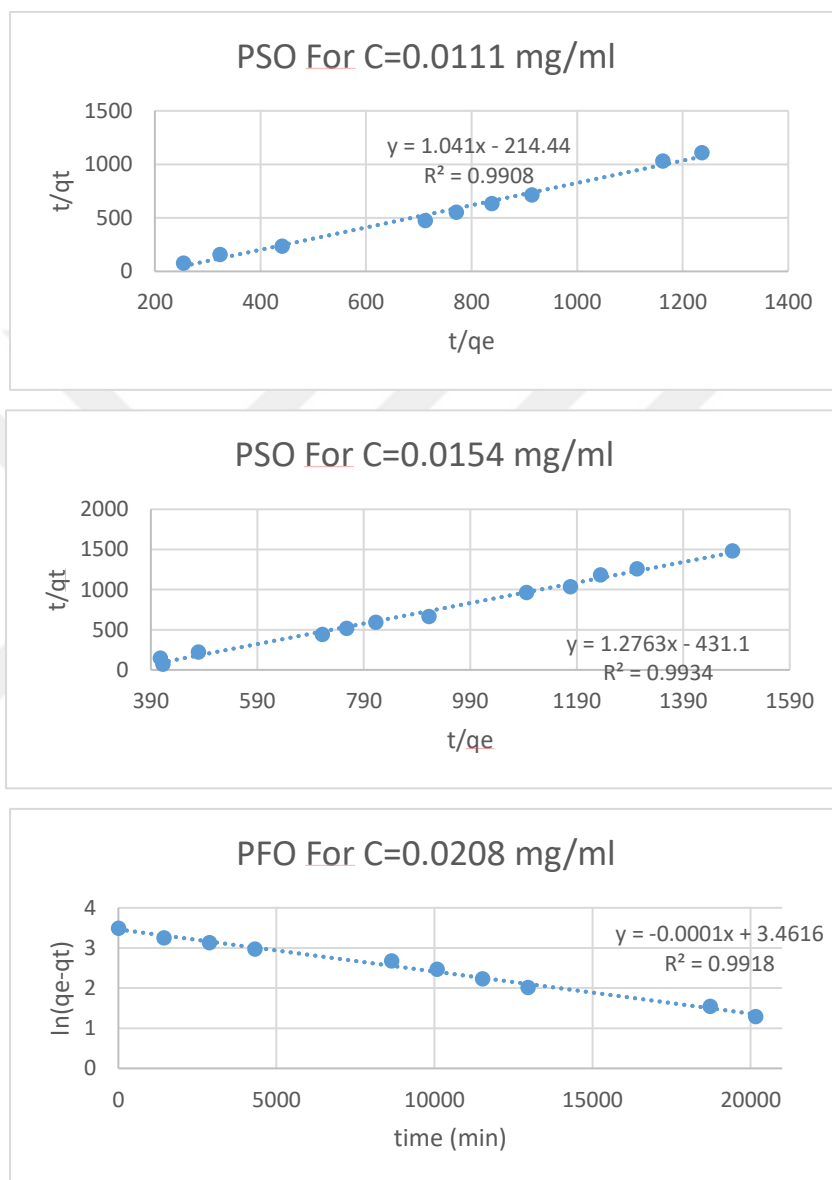


Figure 4.13: Ibuprofen adsorption kinetics of UiO-66 pellets from water at 37°C.

Moreover, for all these IBU adsorption studies, supercritically activated MOF or MOFACs were used. To understand the effect of supercritical activation on adsorption, unactivated UiO-66 pellets were also studied at an ibuprofen concentration of 0.0208 mg/ml and shown in Figure 4.14. The adsorption of ibuprofen took longer (around 29

days) for unactivated pellet when compared to activated one (20 days). But the amount of ibuprofen uptake was the same for both.

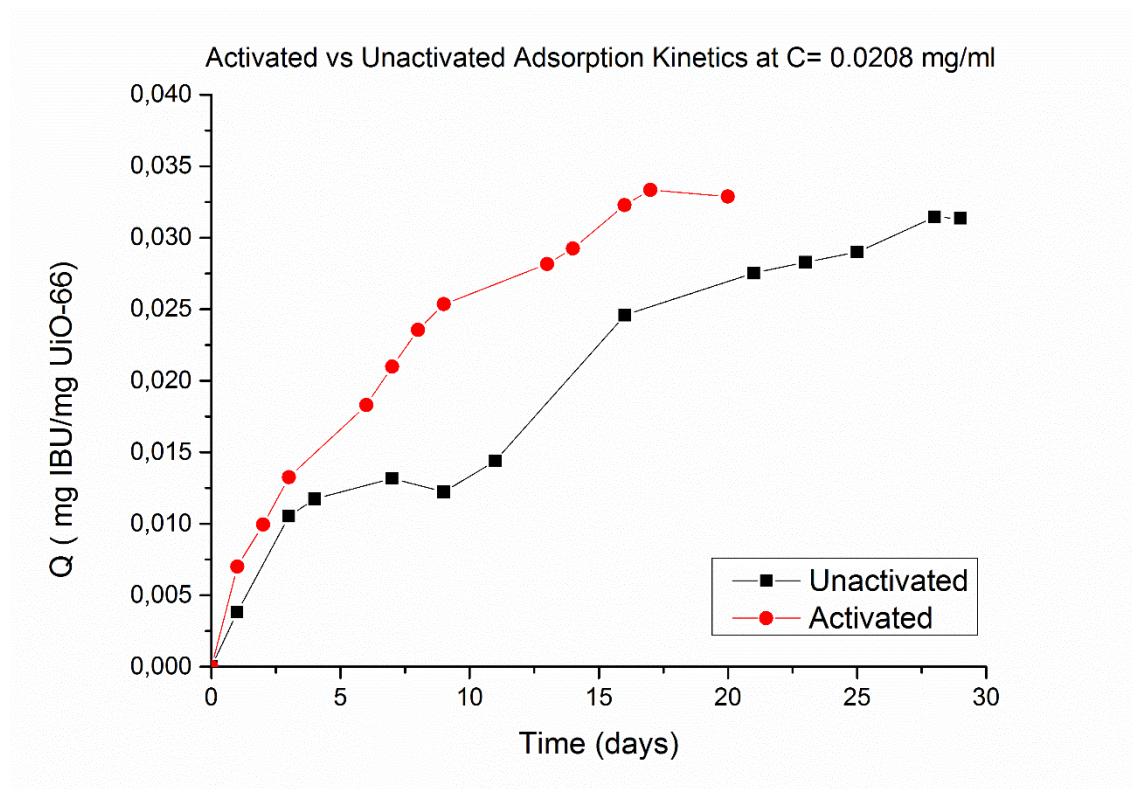


Figure 4.14: Effect of supercritical activation on adsorption of ibuprofen on UiO-66 pellets.

4.4 Drug Release: Paracetamol

4.4.1 Effect of Loading Solutions

A more uniform distribution of the drug throughout the matrix was achieved with higher initial concentrations. This uniformity is expected and clearly discussed by Ulker et al (Ulker & Erkey, 2017). It can also be observed with the initial delivery rates of these systems as shown on Figure 4.15. It was also observed that the profiles of ZIF-8 composite was not much different with loading concentrations although the difference was quite clear for Fe-BTC composite. This difference can be explained by the size of MOF's cages (5.5 and 8.6 Å for Fe-BTC, 6 Å for UiO-66, 3.4 Å in diameter for ZIF-8) and the size of paracetamol (5 Å x 8.7 Å). PC may have been adsorbed into Fe-BTCs' pores but we do not expect any for ZIF-8 due to its aperture and this hydrophobic nature.

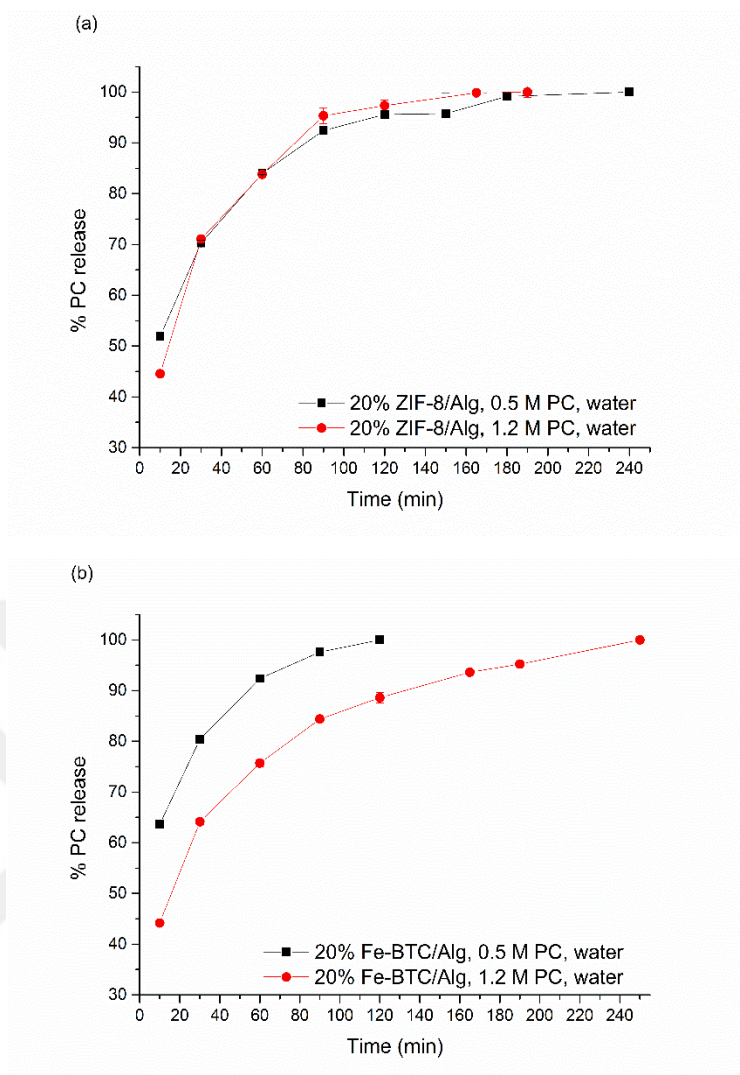


Figure 4.15: Drug release profiles for (a) 20% ZIF-8/Alg and (b) 20% Fe-BTC/Alg comparing two different initial loading concentrations: 0.5 M and 1.2 M.

4.4.2 Effect of Excess Solution

A more uniform drug distribution was also observed for samples with excess solution. Having an excess solution provided a more uniform distribution of the drug throughout the matrix meaning more paracetamol precipitated deeper inside the beads which in turn resulted in lower initial releases compared to non-excess ones. Figure 4.16 depicts the release profiles of composites and alginate comparing presence of excess solutions.

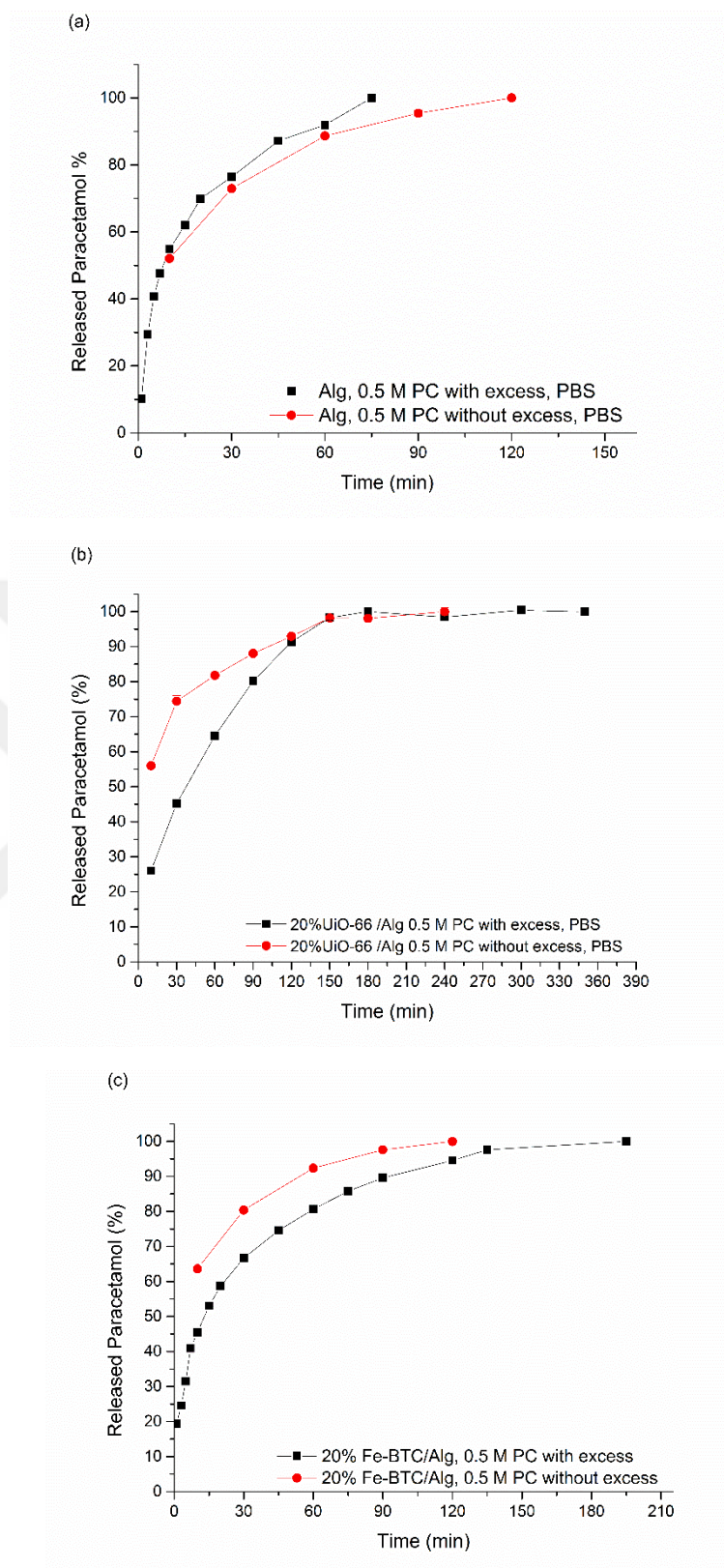
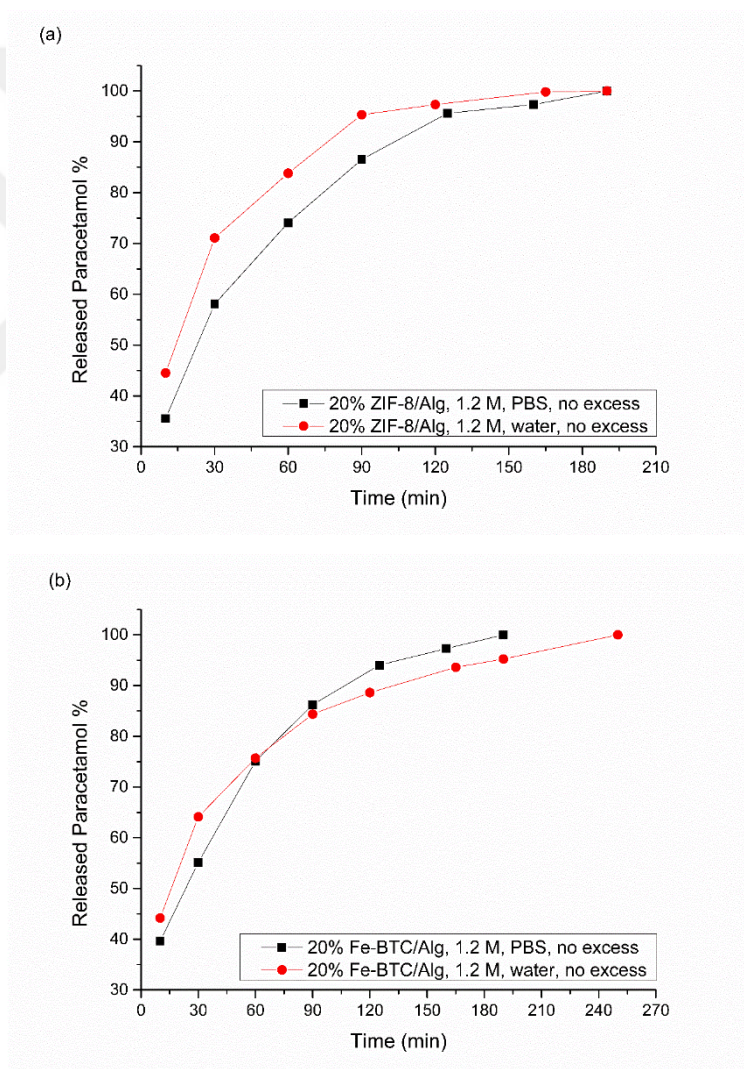


Figure 4.16: Comparison of release profiles for excess and no excess SAS processes (a) Alginate, (b) UiO-66/Alg and (c) Fe-BTC/Alg.

4.4.3 Effect of Release Medium

The effect of release medium was studied. Phosphate buffered saline (PBS) at pH 5.8 or water at neutral pH were used as a release medium. This is due to the fact that many MOFs degrade in PBS buffer which contain phosphate ions that attack the MOFs and result in phosphate insoluble particles. Degradation of UiO-66 and ZIF-8 in PBS were well studied in literature as well as MIL-100(Fe) which is the crystalline form of Fe-BTC (Cunha et al., 2013; X. Li et al., 2017; Velásquez-Hernández et al., 2019). In this context, release of PC in both media were investigated. Figure 4.17 shows the kinetics of PC delivery from 20% (Fe-BTC, ZIF-8)/Ca-Alginate and Ca-Alginate changing the release medium.



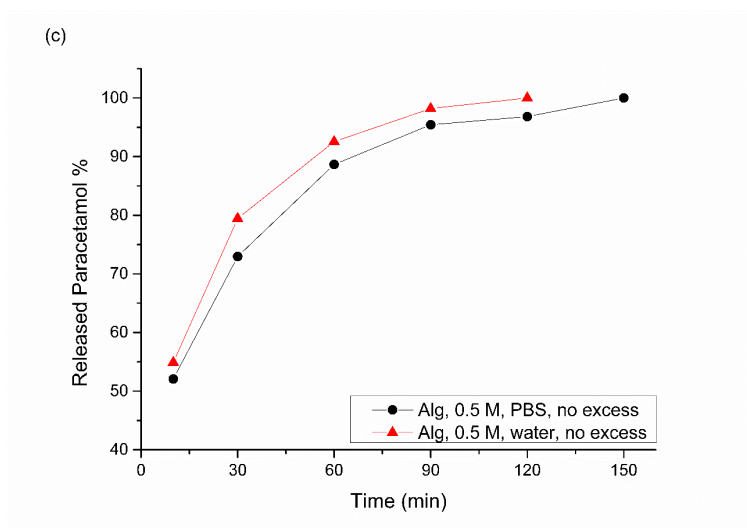


Figure 4.17: Paracetamol release profiles of 20%ZIF-8/Alg (a), 20%Fe-BTC/Alg (b) and Alg (c) in PBS buffer and water.

Comparing the release media, it was observed that there is not much difference in delivery profiles. There are a couple of reasons for this. First, for the PBS medium, the aerogel that surrounds the MOF particles delay the degradation process as it takes time to wet the composites and diffuse in through the alginate's mesopores. Secondly, the MOFs present in these MOFACs are in bulk form. They are not nanoscaled MOFs but rather aggregates. This fact also delays the degradation of MOFs by PBS. Velásquez-Hernández et al. investigated and discussed that nanoZIF-8 degrades faster than micro-ZIF-8 (Velásquez-Hernández et al., 2019). Therefore, paracetamol which is readily soluble in water/ PBS medium at these concentrations was quickly released before the MOF started degrading in PBS medium. Long after the drug was released, the composites degraded in PBS medium as shown on Figure 4.18.

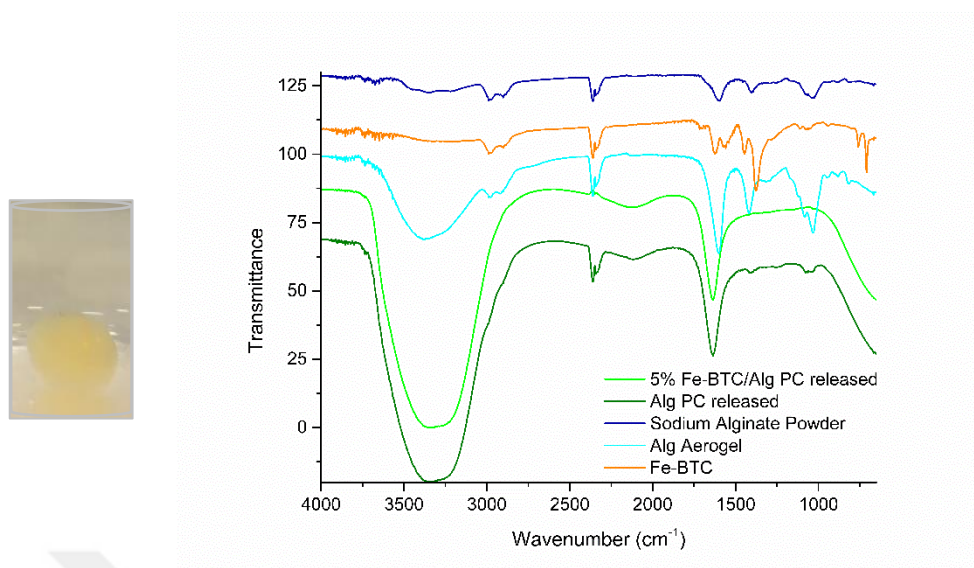


Figure 4.18: FTIR spectra and picture of the composite after the drug is released.

4.4.4 Effect of MOF content

The effect of MOF content on release kinetics was assessed with Fe-BTC/Alginates. All Fe-BTC/Alginates were loaded with 0.5M Paracetamol, having excess solutions and released to PBS medium. Figure 4.19 shows the delay in release profiles with increasing Fe-BTC content. While calcium alginate delivered all of paracetamol in 75 minutes, it took 150 minutes for 5% Fe-BTC/Alg, and 210 minutes for 50% and 70% Fe-BTC/Alg. Presence of Fe-BTC clearly delayed the delivery of the drug and this delay increased with increasing Fe-BTC content. Therefore, a prolonged release was obtained in Fe-BTC/Alg composites compared to pure calcium alginate probably by Fe-BTC acting as a barrier and delaying the diffusion of the drug through its micropores within the hierarchical porous structure.

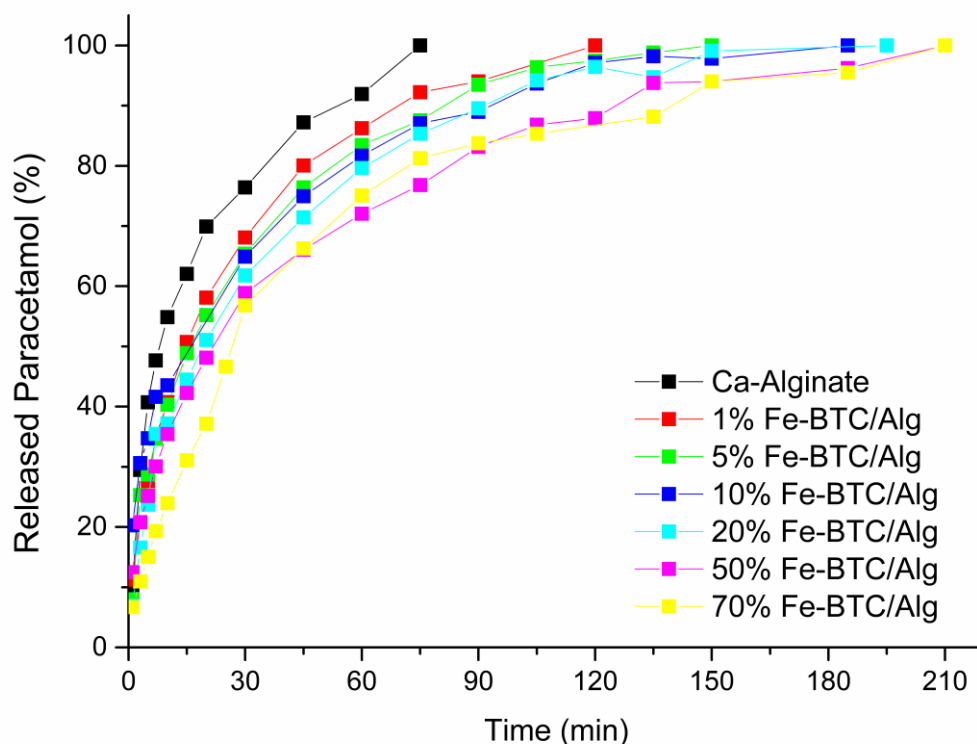


Figure 4.19: Effect of varying Fe-BTC content on release kinetics for Fe-BTC/Ca-Alginate

Although there are no MOF-paracetamol studies to compare these results with, the general release profiles of MOFs take longer delivery times compared to these composites. This is expected as enhanced mass transfer is obtained with the open meso- and macropores of alginate surrounding the MOFs. From alginate side, pure calcium alginate is in line with the literature and we observe a delay in delivery with increasing Fe-BTC content, making these systems very promising for fine tuning.

4.4.5 Material balance closures

The material balances were checked by comparing the expected drug amount found by Equation 3.3 and the amount of drug calculated at the end of the release process by Equation 3.4 using the concentration of paracetamol in the release medium. The material balance closures were depicted in Table 4.6 below.

Table 4.6: Material balance closures for the paracetamol releases

Composites loaded with PC	Expected PC (mg)	Obtained PC from release (mg)	Difference (mg)
20% ZIF-8 /Ca-Alg	34	36.89	-2.89
20% Fe-BTC /Ca-Alg	47.7	50.22	-2.52
20% ZIF-8 /Ca-Alg	37	35.35	1.64
20% Fe-BTC /Ca-Alg	43.3	41.21	2.08
Ca-Alg	16.3	18.26	-1.96
Ca-Alg	16.7	18.94	-2.24
20%UiO-66 /Ca-Alg	16.9	19.07	-2.17
20%UiO-66 /Ca-Alg	8.3	10.27	-1.97
20% ZIF-8 /Ca-Alg	20.2	19.98	0.22
20% Fe-BTC /Ca-Alg	20.32	21.81	-1.49
Ca-Alg	3.05	2.71	0.33
20% ZIF-8 /Ca-Alg	6.29	6.79	-0.50
20%UiO-66 /Ca-Alg	5.54	5.97	-0.43
Ca-Alg	3.08	2.45	0.93
1% Fe-BTC /Ca-Alg	3.25	2.41	1.10
5% Fe-BTC /Ca-Alg	3.02	3.27	0.06
10% Fe-BTC /Ca-Alg	3.26	3.19	0.71
20% Fe-BTC /Ca-Alg	3.26	3.1	0.76
50% Fe-BTC /Ca-Alg	3.22	4.09	-0.32
70% Fe-BTC /Ca-Alg	3.91	4.22	-0.02

4.4.6 Release kinetics from the composites

The release profiles were further fitted into the Korsmeyer- Peppas model which is also known as the Peppas equation to describe the drug release mechanism (Ritger & Peppas, 1987).

$$\frac{M_t}{M_\infty} = kt^n \quad (4.2)$$

For spherical systems as used in this study, the diffusional exponent n with a value 0.43 represents purely Fickian diffusion and n values as low as 0.3 were explained as the polydispersity of the system. Anomalous (non-Fickian) transport was characterized by $0.43 < n < 1.00$ depicting an overlap of different phenomena such as diffusion and polymer

swelling (J Siepmann & Siepmann, 2008). Lastly, $n=1$ is zero-order release. It should be noted that this equation is used extensively to describe the first 60% of the release curves.

All releases fitted very well to Peppas equation with coefficients of determination (R^2) being either 0.98 or 0.99. Table 4.7 summarizes the diffusional exponents of samples calculated using the linearized form of Peppas equation by fitting the release profiles. Generally, paracetamol release kinetics had n values lower than 0.43 meaning purely Fickian diffusion of the drug. Some exceptions were also present showing n values greater than 0.43 depicting anomalous (non-Fickian) transport which can be explained by diffusion and swelling of the composite samples. Interestingly, all the high n valued releases were from excess samples with PBS used as delivery medium. Neither of them were enough to cause the system to swell alone meaning there was a contribution from both the excess condition and the PBS medium to cause the swelling.

Table 4.7: Diffusional exponents of composites calculated using the linearized form of Peppas equation

Sample, loading solution concentration, release medium, excess condition	Diffusional Exponent, n	R^2
Ca-Alg, 0.5M, PBS, excess	0.50	0.99
Ca-Alg, 0.5M, PBS, no excess	0.30	0.99
Ca-Alg, 0.5M, water, no excess	0.30	0.99
1% Fe-BTC /Ca-Alg, 0.5M, PBS, excess	0.52	0.99
5% Fe-BTC /Ca-Alg, 0.5M, PBS, excess	0.52	0.98
10% Fe-BTC /Ca-Alg, 0.5M, PBS, excess	0.42	0.98
20% Fe-BTC /Ca-Alg, 0.5M, PBS, excess	0.39	0.98
50% Fe-BTC /Ca-Alg, 0.5M, PBS, excess	0.45	0.99
70% Fe-BTC /Ca-Alg, 0.5M, PBS, excess	0.62	0.99
20% ZIF-8 /Ca-Alg, 1.2 M, PBS, no excess	0.40	0.99
20% ZIF-8 /Ca-Alg, 1.2 M, Water, no excess	0.34	0.98
20% ZIF-8 /Ca-Alg, 0.5 M, Water, no excess	0.26	0.99
20% Fe-BTC /Ca-Alg, 1.2 M, PBS, no excess	0.35	0.99
20% Fe-BTC /Ca-Alg, 1.2 M, water, no excess	0.29	0.99
20% Fe-BTC /Ca-Alg, 0.5 M, water, no excess	0.20	0.99
20%UiO-66 /Ca-Alg, 0.5M, PBS, excess	0.50	0.99
20%UiO-66 /Ca-Alg, 0.5M, PBS, no excess	0.20	0.98

4.5 Drug Release: Ibuprofen

All ibuprofen releases were done to distilled water at 37°C under constant stirring inside the oven. PBS was not used on purpose since both UiO-66 and ZIF-8 degrade in PBS (10 mM phosphate ions). MOF drug deliveries are usually performed in either aqueous conditions (simulated cutaneous conditions) or simulated body fluid (SBF) which contain less phosphate (1 mM HPO_4^{2-}). The pH of the release medium was not adjusted. As ibuprofen is a weak acid, the release medium's pH gradually came to around ~4.

4.5.1 Effect of calcium and zinc as alginate crosslinkers

Ibuprofen loaded calcium alginate and zinc alginate beads were compared in order to understand the effect of alginate crosslinkers. The results showed that the difference between Ca-Alginate and Zn-Alginate in terms of ibuprofen release rate is considerable. Although the initial rates are almost the same, while it took 40 hours for calcium alginate to release its ibuprofen fully, it took almost 200 hours for zinc alginate as shown in Figure 4.20. This was explained by Pillay et al. as a greater degree of polymeric crosslinking and reduced hydration with Zn^{2+} (Pillay, Danckwerts, Muhidinov, & Fassihi, 2008). The lower coordination number of Zn^{2+} (4–6) would lower its water attracting power and significantly retard hydration of polymer, as opposed to Ca^{2+} (7–9). This explains the difference in ibuprofen delivery rates and can be used as an effective tool for use of alginate aerogels in the purpose of drug delivery. The same effect was observed for IBU loaded 50%ZIF/Alg composites and shown in Figure 4.21.

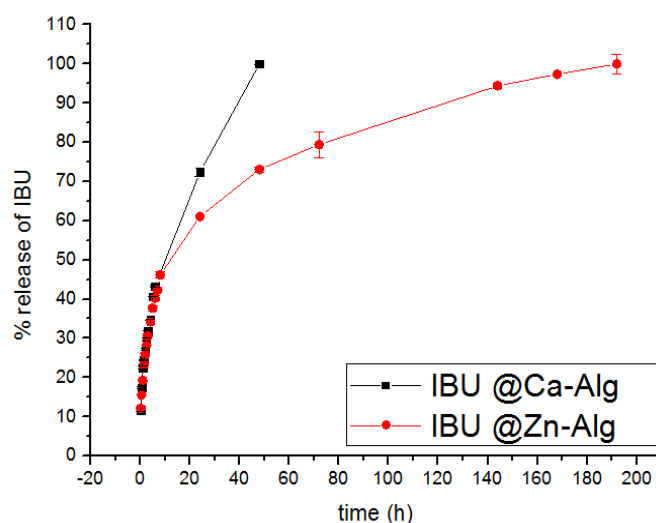


Figure 4.20: The comparison of Ca-Alg and Zn-Alg on the kinetics of ibuprofen release

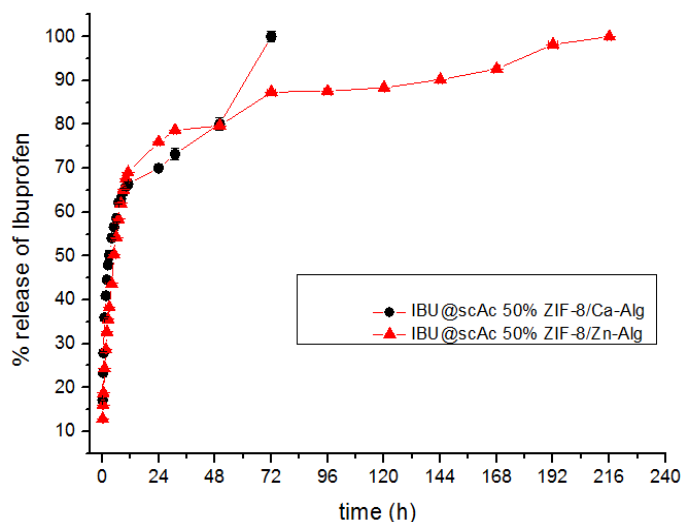


Figure 4.21: The comparison of 50%ZIF/Ca-Alg and 50%ZIF/Zn-Alg on the kinetics of ibuprofen release

4.5.2 Effect of MOF content: ZIF-8/Algs

ZIF-8/Alginate composites were compared in terms of their MOF amounts. It was observed that Ca-Alg and 20% ZIF-8/Alginate releases were almost same, it took 2 days to complete the ibuprofen delivery. For higher MOF contents, a significant delay in delivery was observed. It took 3 days to complete ibuprofen delivery for 50% ZIF-8/Alg and 8 days for 75%ZIF-8/Alg to deliver its drug fully as shown in Figure 4.22.

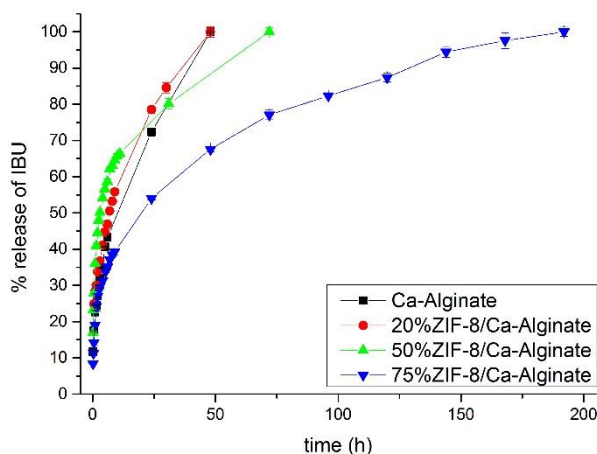


Figure 4.22: Effect of varying ZIF-8 content on ibuprofen release kinetics

This result was found to be promising as increasing ZIF-8 amount clearly delayed the delivery of the drug. Both the initial delivery rate and the overall rate of drug release

decreased for 75% ZIF-8/Ca-Alginates. The material balance closures were satisfying as well, meaning all the ibuprofen adsorbed on the composites were delivered to the release medium.

4.5.3 Effect of MOF content: UiO-66/Algs

UiO-66/Alginate composites were compared in terms of their MOF amounts. For 10 and 20% UiO/Alg's, it took up to 4-5 days to fully release the drugs inside the composite beads. However, for 50% and 75% UiO/Algs, drug release profiles were unexpected. These composites did not release their ibuprofen. Therefore for these systems, no mass balance closures were possible. Due to this, ibuprofen percent releases are given based on expected ibuprofen amounts in Figure 4.23. While 50%UiO/Alg released only 40% of the ibuprofen it had, 75%UiO/Alg released only 10% of the ibuprofen it contained meaning ibuprofen is strongly adsorbed on UiO/Alg composites. The slow and partial release was expected as Rojas et al. released $81 \pm 6\%$ of its ibuprofen from UiO-66 in 7 days (Sara Rojas et al., 2018). However, when Lin et al. studied the adsorption mechanism of ibuprofen on UiO-66, they found out that a synergetic effect of chemical adsorption and π - π interactions. The study revealed that the incomplete-coordinated cationic Zr in the MOF cluster showed high affinity for the anionic ibuprofen resulting in chemisorption as well as π - π interactions between the benzene rings of ibuprofen and UiO-66 both resulting in high binding energies and adsorption capacities (Lin, Zhao, & Yun, 2018).

Moreover, in these high UiO content composites (50 and 75%), UiO-66 release was experienced. Although a calibration curve was not prepared to quantify the MOF, it was reproducible and the intensity of the product is given in Figure 4.24 as area under the curve from HPLC.

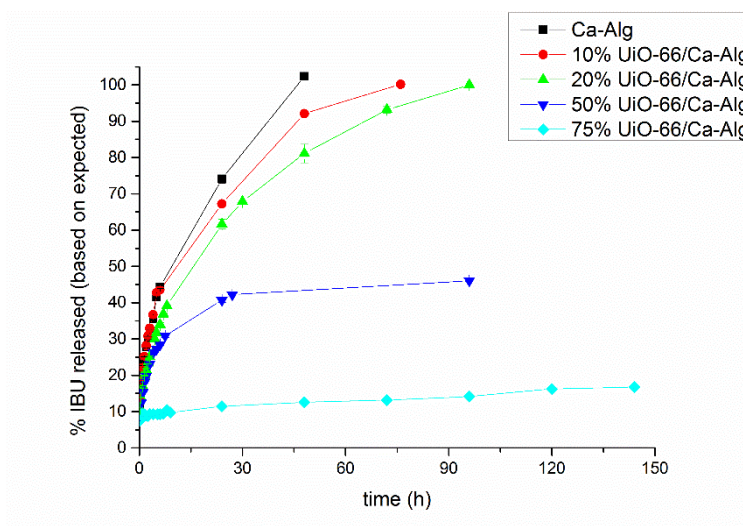


Figure 4.23: Effect of varying UiO-66 content on ibuprofen release kinetics based on expected ibuprofen releases

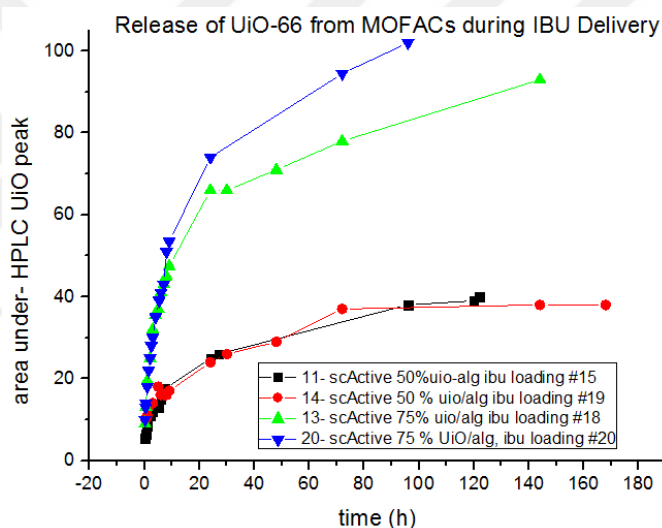


Figure 4.24: Release of UiO-66 from 50 and 75% UiO/Alg composites

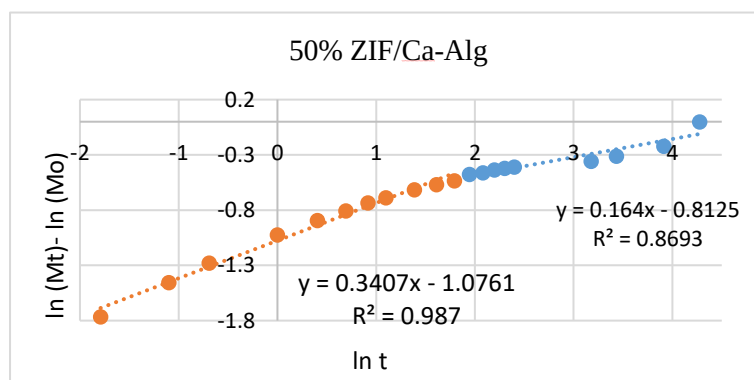
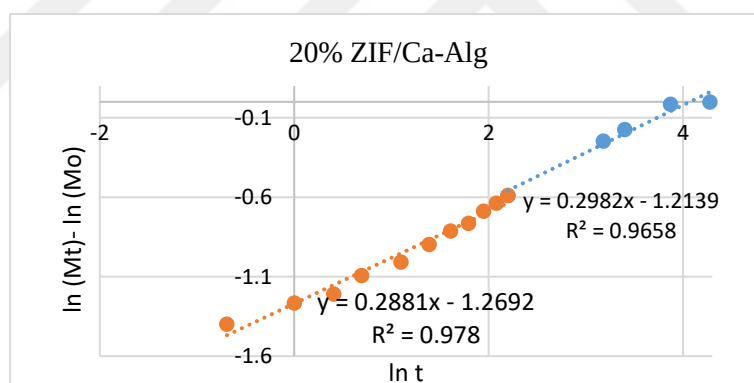
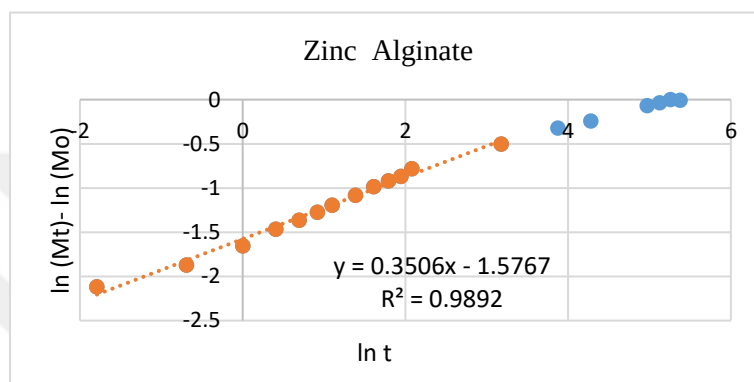
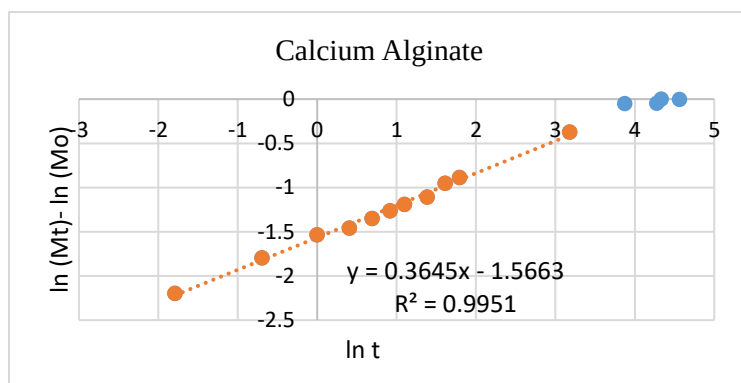
4.5.4 Release kinetics from the composites

For mathematical modeling of ibuprofen deliveries, the release kinetics from the composites were fitted to Peppas equation in linearized form.

$$\ln(M_t) - \ln(M_\infty) = \ln(k) + n \cdot \ln(t) \quad (4.3)$$

The ZIF/Alg results fit well to the Peppas equation, showing purely Fickian diffusion for the first 60% of the releases (shown in orange in Figure 4.25). n was expected to be 0.43 for spherical systems as used here and below 0.43, as low as 0.3 was explained as polydispersity of the system. UiO/Alg composites were not included for modelling due to lack of mass balance closures but further investigated for adsorption in water as a

medium.



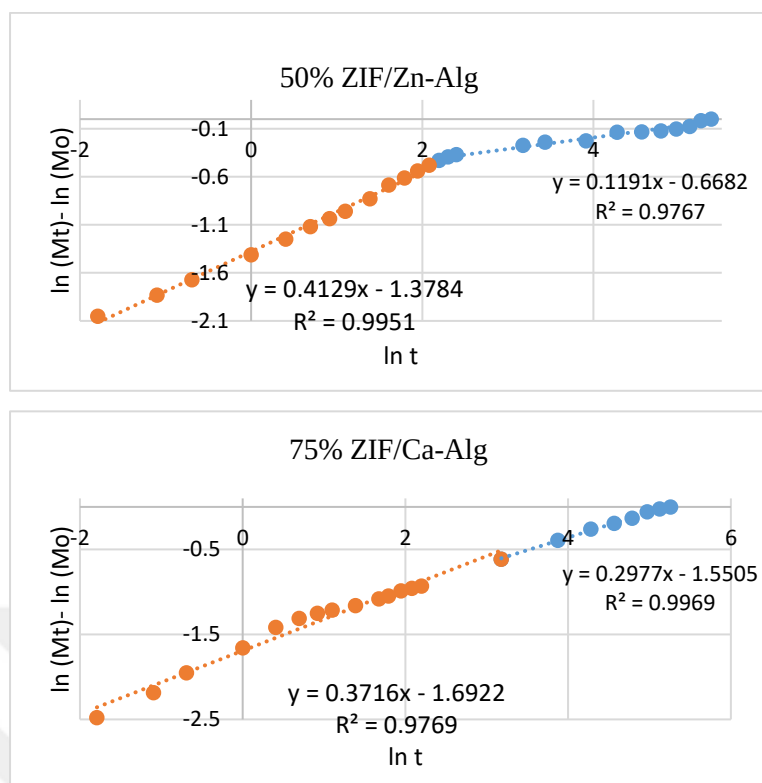


Figure 4.25: Release kinetics fitted to Peppas equation in linearized form

4.6 In situ ZIF-8 synthesis on zinc alginate

Some in situ MOF synthesis studies on alginates were conducted. By adding $\text{Zn}(\text{NO}_3)_2$ and organic linker HMIM to zinc crosslinked alginate, ZIF-8 was synthesized in situ on zinc alginate. MOF crystals formed mainly on the external surface rather than inside the alginates pores as shown in Figure 4.26 meaning that the metal and the organic linker reacted before they reached the pores of alginate.

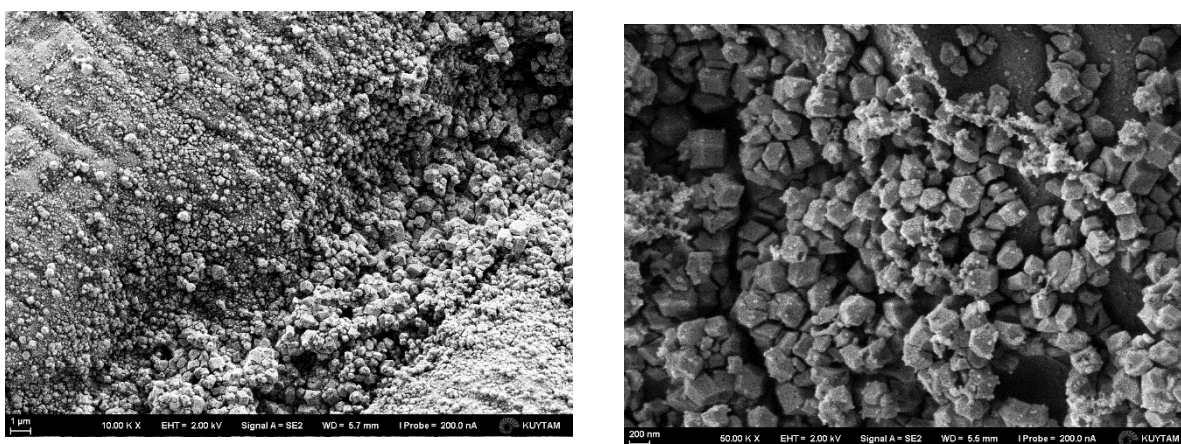


Figure 4.26: SEM images of in situ synthesized ZIF-8 on outer surface of zinc alginate

The presence of ZIF-8 crystals on the external surface of the composite beads were also observed on the XRD spectra shown in Figure 4.27.

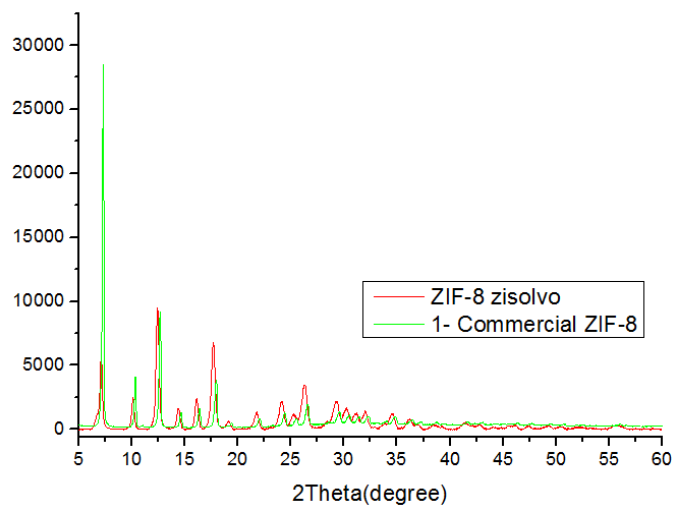


Figure 4.27: XRD spectra of in situ synthesized ZIF-8 compared with commercial pristine ZIF-8

The in situ synthesized ZIF-8/Zn-Alginate was also loaded with ibuprofen under the same conditions. The loaded ibuprofen was then released to water and compared with Zn-Alginate. The results shown in Figure 4.28 depicts that the release profile is similar to Zn-Alginate except the initial drug amount that is released. There is more ibuprofen on the external surface of in situ ZIF-8/Zn-Alginate composite that is released initially. This was expected as the synthesized ZIF-8 is mainly on the outer surface of the composite and the ibuprofen loaded was adsorbed on the outer surface.

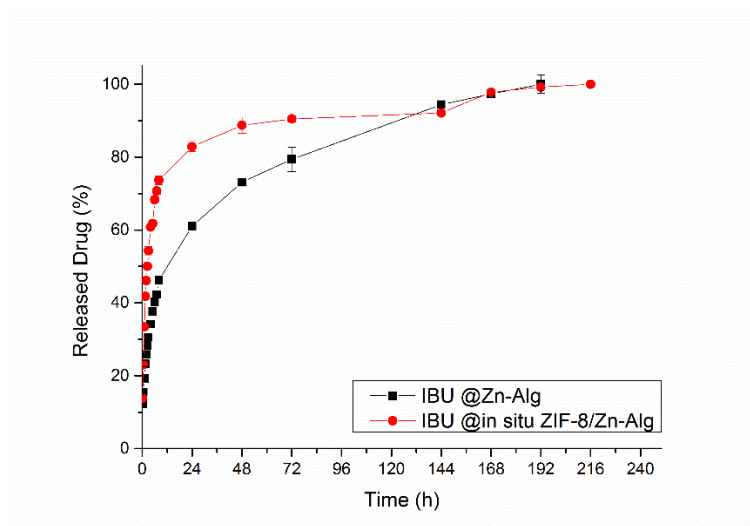


Figure 4.28: The comparison of in situ ZIF-8/Zn-Alg and Zn-Alg on the kinetics of ibuprofen release

4.7 Gas adsorption experiments of UiO-66/Alg and ZIF-8/Alg

Gas adsorption experiments were also conducted on 75%UiO-66/Alginate and 75%ZIF-8/Alginate. A Micromeritics (Particulate Systems) High Pressure Volumetric Analyzer HPVA II-200 was used for measuring CH₄, CO₂ and N₂ adsorption isotherms at 25 °C in a pressure range of 0.1–1 bar. Samples of 100 mg were used for each measurement.

The samples were degassed for approximately 12 h under vacuum at 125 °C in the degas port. Before the analysis, the sample holder was purged with He in the analysis port. CH₄, CO₂ and N₂ adsorption isotherms obtained are shown in

Figure 4.29 for ZIF-8/Alg and Figure 4.30 for UiO-66/Alg.

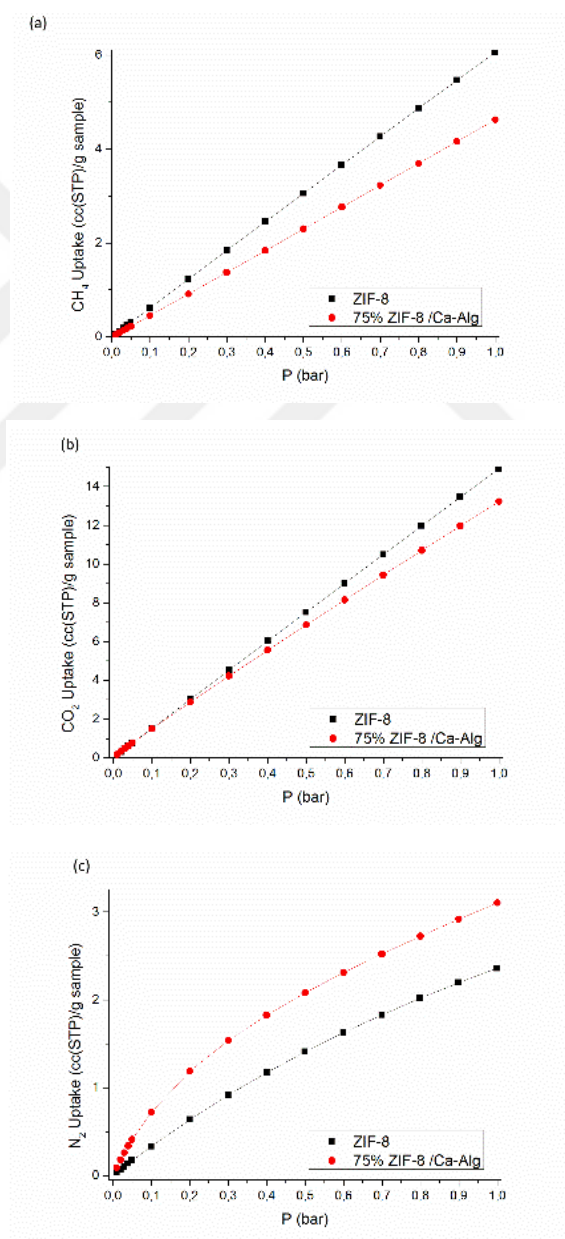


Figure 4.29: CH₄ (a), CO₂ (b) and N₂ (c) adsorption isotherms of 75%ZIF-8/Alginate at 25 °C.

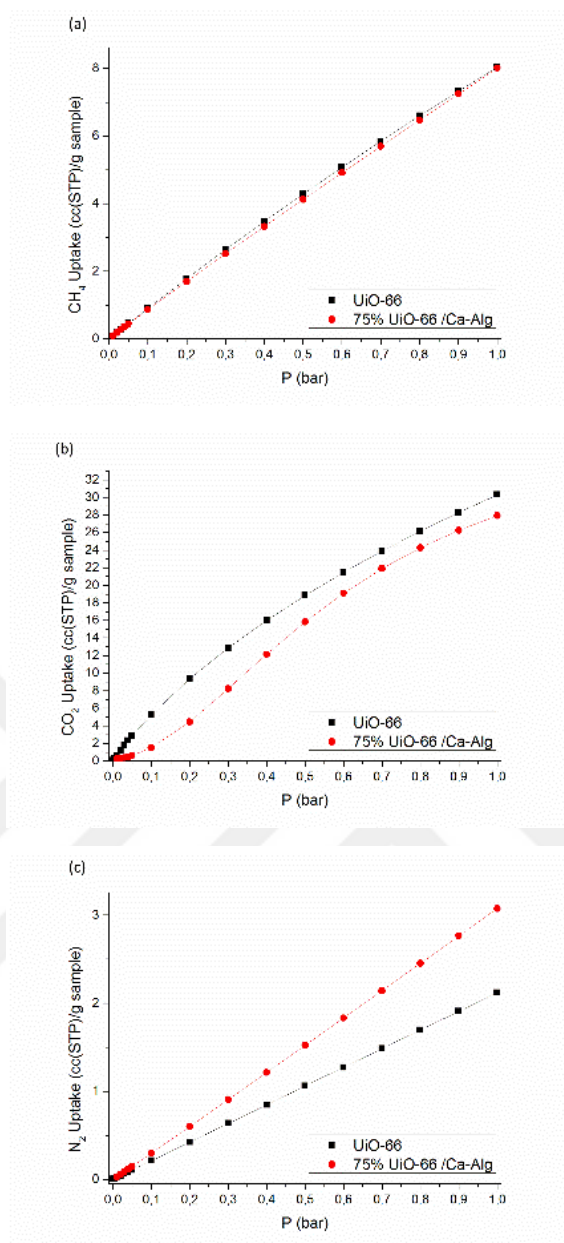


Figure 4.30: CH₄ (a), CO₂ (b) and N₂ (c) adsorption isotherms of 75%UiO-66/Alginate at 25 °C.

75% MOF containing MOFACs showed quite good gas adsorption capacities when compared to their pristine counterparts. The composites can be promising for adsorption of several gases as they eliminate the pressure drop by providing a meso-/macroporous matrix around the microporous and powdered MOFs without reducing the adsorptive capacity.

Chapter 5: Conclusion

MOFACs are hierarchically multimodal porous materials with favorable properties which makes them promising for drug delivery applications. In this study, novel MOFACs comprised of three types of MOFs (Fe-BTC, ZIF-8 or UiO-66) and calcium or zinc alginate were synthesized by combining simple mixing with dripping technique. The synthesized composites were then loaded with paracetamol and ibuprofen. Paracetamol was loaded from ethanolic solutions via SAS (supercritical antisolvent precipitation) inside the pores whereas ibuprofen was loaded from supercritical CO₂ solutions. The factors that affect the loading amount and distribution of the drug inside the composite matrix were investigated. Paracetamol loadings were found to be highly dependent on and limited by the drug concentration in ethanolic loading solutions as well as having excess solutions in the extraction vessel prior to supercritical drying. Almost 70 wt% paracetamol loadings were achieved with 1.2 M loading solutions and having excess solutions. Around 20 wt% ibuprofen loadings were achieved from supercritical CO₂ solutions which was in line with the literature.

The release behavior of the drugs from the composite matrices to PBS buffer or distilled water were investigated. It was shown that the Fe-BTC/Alginate composites were promising for paracetamol delivery and ZIF-8/Alginate composites were found to be promising for ibuprofen delivery. The release delaying ability of both systems can be fine-tuned by changing the amount of MOF content in the composites. UiO-66/Alginate composites were not able to release the adsorbed ibuprofen therefore were not promising for drug delivery. An in situ ZIF-8/Zn-Alginate composite was also synthesized and loaded with ibuprofen. ZIF-8 was found mainly on the external shell of the composite beads. Its release study showed a higher initial release rate due to ibuprofen desorption from the external surface. Furthermore, the release kinetics were fitted into Korsmeyer-Peppas model. It was found that Fickian diffusion is the main transport mechanism while some PBS systems with excess solutions also showed swelling behavior.

Lastly, 75% ZIF-8 or UiO-66 containing Ca-Alginate MOFACs were studied for adsorption of CH₄, CO₂ and N₂ and their adsorption isotherms at 25 °C in a pressure range of 0.1–1 bar were measured. The study showed that these composites were promising for further gas adsorption studies.

Overall, incorporating microporous MOFs into mesoporous aerogel matrices to make MOF/aerogel composites is a promising strategy to achieve highly desirable materials where hierarchical micro-/mesoporosity can be easily controlled or tuned. In this thesis, these materials were studied for drug delivery purposes and found to be promising for further studies.



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Appendix A

Comparison of Ibuprofen loadings of MOFACs with MOFs and aerogels in the literature

